BE

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12187 A2

(51) International Patent Classification[7]: A61K 31/404

(21) International Application Number: PCT/GB00/03140

(22) International Filing Date: 14 August 2000 (14.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9919411.0 18 August 1999 (18.08.1999) GB

(71) Applicant (*for all designated States except MG, US*): **ASTRAZENECA AB** [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **HARGREAVES, Rodney, Brian** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **WHITTAMORE, Paul, Robert, Owen** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agents: **BROWN, Andrew, Stephen** et al.; Astrazeneca, Global Intellectual Property, Alderley Park, P.O. Box 272, Mereside, Macclesfield, Cheshire SK10 4GR (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

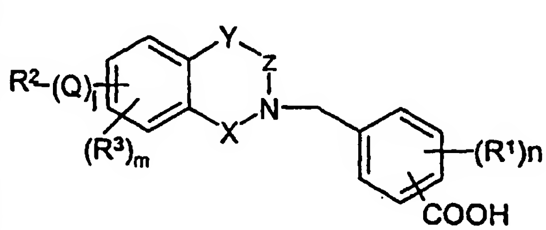
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/12187 A2

(54) Title: CHEMICAL COMPOUNDS



(I)

(57) **Abstract:** The present invention relates to the use of certain benzoic acid derivatives of formula (I), where the substituents are as defined in the specification, which act as peroxisome proliferator activated receptor (PPAR) agonists, in particular gamma receptors (PPARγ), and so are useful in the treatment of states of insulin resistance, including type 2 diabetes mellitus.

CHEMICAL COMPOUNDS

The present invention relates to the use of certain benzoic acid derivatives which act as peroxisome proliferator activated receptor (PPAR) agonists, in particular gamma receptors (PPARγ), and so are useful in the treatment of states of insulin resistance, including type 2 diabetes mellitus. Novel pharmaceutical compositions and novel compounds are also defined, together with methods of their production.

Traditionally, therapeutic intervention in type 2 diabetes has had a 'glucocentric focus' dominated by the use of insulin secretogogues e.g. the sulphonylureas and the measurement of glycated haemoglobin (HbA1c) or fasting blood sugar level (FPG) as indices of diabetic control. In the USA, patients with type 2 diabetes are usually treated with diet and, when needed, a sulphonylurea compound. However, it is estimated that approximately 30% of patients initially treated with sulphonylurea agents have a poor response and in the remaining 70%, the subsequent failure rate is approximately 4-5% per annum. Other estimates put failure rates higher with few patients responding after 10 years therapy. A treatment-related increase in body weight is also experienced with these agents. Prior to the FDA approval of metformin in 1995, the only therapeutic option for type 2 diabetic patients, in whom sulphonylurea therapy had failed, was insulin.

Despite the introduction of newer agents both the incidence and prevalence of type 2 diabetes continues to increase on a global basis. Approximately 16 million people in the USA have diabetes mellitus, 90-95% of whom have type 2 disease. This represents an enormous healthcare burden; estimated in 1998 to be some $98 billion per annum in direct and indirect healthcare costs. Recently, both the ADA and WHO have revised guidelines for the diagnosis of diabetes and classified diabetes more according to aetiology. The threshold for diagnosis (FPG > 126mg/dl) has been lowered and the term 'type 2' is now used to describe mature onset diabetics who have not progressed to insulin therapy. After the ADA implemented these new criteria in 1997, the prevalence of the type 2 disease sector increased by nearly 6 million people in the seven major pharmaceutical markets (France, Germany, Italy, Japan, Spain, UK and USA).

Apart from often mild acute symptoms, type 2 diabetics are also at a considerable risk of developing long term complications of the disease. These include a 4-5 fold higher risk, (compared with non-diabetics), of developing macrovasular disease including CHD and PVD and microvascular complications including retinopathy, nephropathy and neuropathy. In many individuals, overt type 2 diabetes is preceded by a period of reduced insulin sensitivity (insulin

resistance), accompanied by a cluster of other cardiovascular risk factors, collectively termed as insulin resistance syndrome (IRS).

It has been estimated that approximately 80% of type 2 diabetics are obese and other co-morbidities of the IRS include: dyslipidemia, hyperinsulinemia, raised arterial blood pressure, uricemia and a reduced fibrinolysis. Given the increased global prevalence and incidence of type 2 diabetes and the very high costs of treating the long term complications of the disease there is tremendous interest in the development of agents that delay or prevent the onset of type 2 diabetes and in those that reduce the risk of cardiovascular complications associated with IRS. These activities have lead to the introduction of the thiazolidinedione (TZD) class of insulin sensitisers that improved the dyslipidemia and thus restored the insulin sensitivity leading to improved glycemic control and lower HbA1c levels.

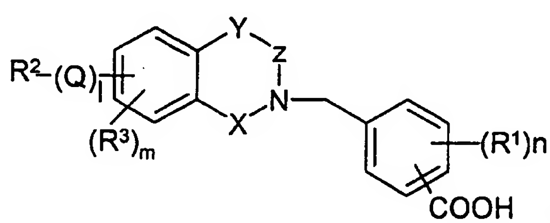
Although the complex interplay between lipids and carbohydrates as metabolic fuels has been recognised for many decades it is only recently, that researchers and clinicians have begun to focus on the importance of dyslipidemia seen in type 2 diabetes. Much has been made of the relative sensitivities of muscle, liver and adipose tissues to insulin and a case for the primacy of insulin resistance in adipose tissue leading to the IRS has been debated. A typical dyslipidemic atherogenic lipoprotein phenotype (referred to as type B) is seen in IRS including frequently in type 2 diabetics, characterised by a modestly raised LDL-C, a more significant increase in VLDL-TG and reduced HDL. Apparently, changes in the physicochemical properties of VLDL-TG particles result in slower plasma clearance rates and in the generation of small dense LDL particles. The latter permeate the vascular endothelium more readily and are more prone to oxidation and glycation and are considered to play a critical role in atherogenesis in large vessels. Although more difficult to measure, improved free fatty acid (IFFA) flux is increasingly considered to play an important role in the IRS affecting metabolic events in muscle, liver, adipose tissue and pancreas.

The first generation TZDs e.g. troglitazone, pioglitazone, rosiglitazone were in clinical development before the putative mechanism of action was discovered and published in 1995 (PPARγ activation). It is clear from experience with these first generation agents that it is difficult to predict from animal pharmacology the safety and efficacy profile these agents will have in the clinic. Thus, knowledge of the putative mechanism of action of this class coupled with concerns regarding safety, offers the opportunity to identify non-TZD activators of PPAR for the treatment of type 2 diabetes and is the subject of this invention. Furthermore, we recognise that agents with a dual action at both α and g PPAR may have additional benefits in

reducing diabetic co-morbidities, particularly raised triglycerides. Such agents may be useful in the treatment of type 2 diabetes, the IRS, dyslipidemia and in reducing risk of cardiovascular disease.

US Patent No 5151435 and EP-A-517357 describe the use of certain indole derivatives as angiotensin II antagonists. WO9808818 describes the use of *inter alia* other indole derivatives as phospholipase inhibitors. Tetrahydroisoquinoline derivatives useful as thromboxane A2 antagonists are described in EP-A-300725.

The present invention provides the use of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt or ester thereof, in the preparation of a medicament for use in the activation of PPAR,

X, Y and Z may represent either bonds or atoms or groups of atoms such that X, Y and Z together with the nitrogen atom complete an optionally substituted five or six-membered aromatic or non-aromatic ring;

where each R^1 is selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl, C_{1-3}alkoxy, optionally substituted hydrocarbyl or optionally substituted heterocyclyl and n is 0, 1 or 2;

R^2 is selected from R^4, OQR^4, $C(O)_pR^4$, $S(O)_qR^4$, $N(QR^6)R^7$, halo, cyano, carboxy, nitro, $(O)CN(QR^6)R^7$, $OC(O)N(QR^6)R^7$, $NR^5C(O)_pR^6$, $NR^5CON(QR^6)R^7$, $NR^5CSN(QR^6)R^7$, $NR^5C(O)OR^6$, $N{=}CR^6R^7$, $S(O)_qN(QR^6)R^7$ or $NR^5S(O)_qR^6$, or R^2 is carboxy, $CH{=}CHQR^4$ or $NR^5C(O)C(O)R^6$;

where p is 1 or 2, q is 0, 1, 2 or 3;

R^4 is selected from optionally substituted hydrocarbyl or optionally substituted Qheterocyclyl groups;

R^5, R^6 and R^7 are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted Qheterocyclyl groups or R^6 and R^7 together with the atom to which they are attached form a ring which may be optionally substituted and which may comprise one or more heteroatoms;

l is 0 or 1;

each Q is independantly selected from a direct bond, C_{1-3}alkylene or C_{2-3}alkenylene;

each R^3 is independently selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl, C_{1-3}alkoxy and m is 0, 1 or 2.

As used herein, the term "hydrocarbyl" refers to alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl groups.

The term "heterocyclyl" refers to single or fused ring structures which, unless stated otherwise, may be aromatic or non-aromatic in nature and which suitably contain from 2 to 20 ring atoms, suitably from 5 to 8 ring atoms, at least one of which and suitably up to four of which are heteroatoms. The term "heteroatom" includes oxygen, sulphur and nitrogen. Where a heteroatom is nitrogen, it will be further substituted for example by hydrogen or an alkyl group. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character.

In this specification the term "aryl" refers to phenyl, biphenyl and naphthyl.

In this specification the term "alkyl" when used either alone or as a suffix includes straight chained, branched structures. These groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms, suitably from 3 to 20 carbon atoms and preferably from 3 to 7 carbon atoms. Terms such as "alkoxy" and "thioalkyl" comprise alkyl groups as is understood in the art.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocylic groups such as phenyl and naphthyl. The term "aralkyl" refers to alkyl groups substituted with aryl, such as benzyl.

Preferably l is 1.

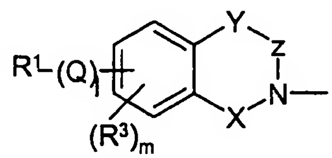
Preferably n is 0 or 1. Ideally n is 0.

Preferably m is 0 or 1. Ideally m is 0.

Preferably R^1 is selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl and C_{1-3}alkoxy.

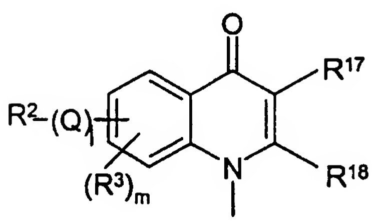
Suitably in the compounds of formula (I), X is a bond or a group CH_2 or C(O); and -Y-Z- is selected from $-CR^{17}=CR^{18}-$, $-C(O)-CR^{17}=CR^{18}-$,

$-CR^{17}=CR^{18}C(O)-$, $-CHR^{17}-CHR^{18}-C(O)-$, $-CHR^{17}-CHR^{18}-CHR^{19}-$, where R^{17}, R^{18} and R^{19} are independently selected from hydrogen or C_{1-3} alkyl such as methyl. Thus, in formula (I), the Group of sub formula (a)

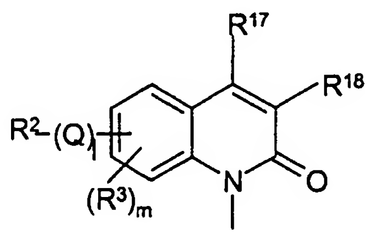


(a)

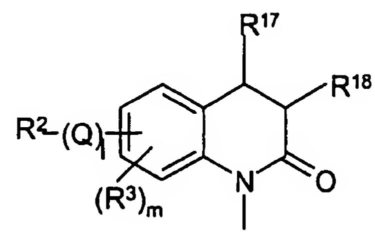
is suitably selected from a group of sub-formula (b), (c), (d), (e), (f), (g), (h) or (i).



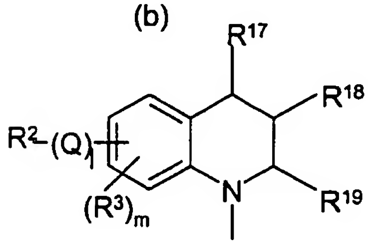
(b)



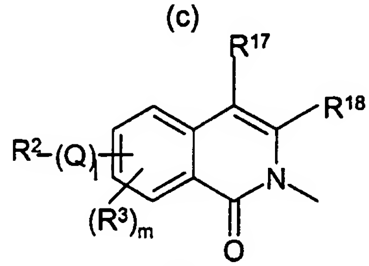
(c)



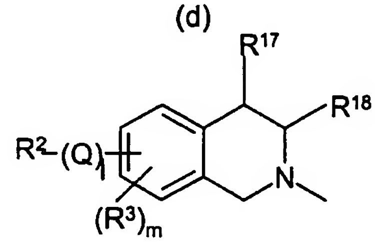
(d)



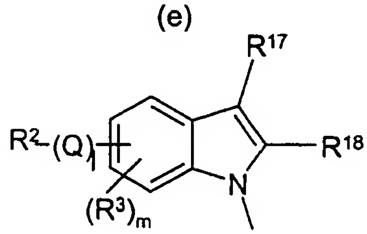
(e)



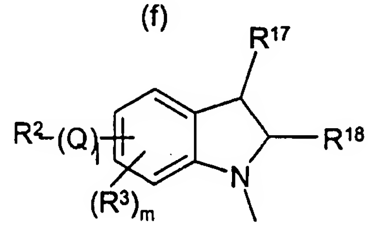
(f)



(g)



(h)

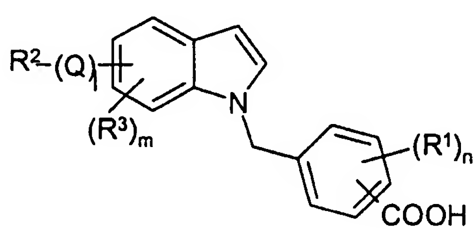


(i)

where R^2, Q, l, R^3 and m are as defined in relation to formula (I).

R^{17}, R^{18} and R^{19} are selected from hydrogen and C_{1-5}alkyl. Preferably R^{17}, R^{18} and R^{19} are all hydrogen.

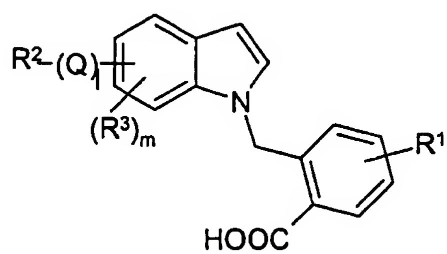
Preferably compounds of formula (I) are indoles of formula (II)



(II)

Wherein A, R^1, R^2, R^3, m and n are as defined above.

The carboxyl group of formula (I) is suitably at the ortho position on the phenyl ring. Thus in the case of the indoles, a particular preferred group of compounds are those of formula (IIA)

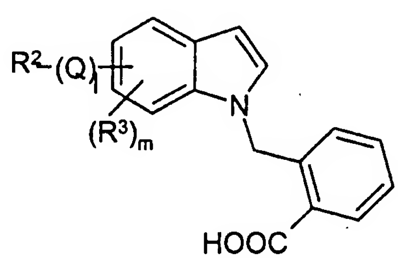


(IIA)

Where present, in the compound of formula (I), (II) or (IIA) R^1 and R^3 are suitably independently selected from halo, methyl and trifluoromethyl, and are preferably halo. Most preferably however, n and m are 0.

Suitable optional substitutents for the heterocyclyl group include carboxyalkyl or carboxyalkenyl.

Thus a particularly preferred group of compounds of formula (IIA) are compounds of formula (III)



(III)

where A and R^2 are as defined above.

Suitable optional substituents on the five or six membered aromatic or non-aromatic ring formed by X, Y and Z are C_{1-5}alkyl, halo, haloC_{1-5}alkyl, =O, hydroxy, carboxy and C_{1-4}alkoxy. Preferably X, Y and Z are unsubstututed or substituted by C_{1-5}alkyl.

Suitable optional substitutents for any hydrocarbyl groups within R^1, R^4, R^5, R^6 and R^7 include halo, cyano, nitro, $C(O)_aR^8$, OR^8, $S(O)_bR^8$, NR^9R^{10}, $C(O)NR^9R^{10}$, $OC(O)NR^9R^{10}$, $NR^8C(O)_aR^9$, $NR^8CONR^9R^{10}$, $N{=}CR^9R^{10}$, $S(O)_bNR^9R^{10}$ or $NR^8S(O)_bR^{10}$ where R^8, R^9 and R^{10}

are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl, any of which may themselves be optionally substituted, a is 1 or 2 and b is 0, 1, 2 or 3.

Suitable optional substitutents for any heterocyclyl groups within R^1, R^4, R^5, R^6 and R^7 include those listed above for hydrocarbyl groups, as well as alkyl, alkenyl or alkynyl groups which may be optionally substituted, for example with halo, cyano, nitro, $C(O)_aR^{11}$, OR^{11}, $S(O)_bR^{11}$, $NR^{12}R^{13}$, $C(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{13}$, $NR^{11}C(O)_aR^{12}$, $NR^{11}CONR^{12}R^{13}$, $N{=}CR^{12}R^{13}$, $S(O)_bNR^{12}R^{13}$ or $NR^{11}S(O)_bR^{12}$ where R^{11}, R^{12} and R^{13} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl, and a and b are as defined above.

Suitable optional substituents for alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl groups within R^8, R^9 and R^{10} include halo, nitro cyano, alkanoyl such as acetyl, oxo, carboxy or salts or esters thereof, alkoxy such as methoxy, ethoxy or propoxy, aryloxy such as phenoxy, thioalkyl such as thiomethyl, thioethyl or thiopropyl, sulphate, haloalkyl such as trifluoromethyl, aryl such as phenyl, carbamate, amino, mono- or di-alkyl amino such as methylamino or di-methylamino. Aryl, heterocyclyl or aralkyl groups R^8, R^9 and R^{10} may further be substituted by alkyl, alkenyl or alkynyl groups suitably having from 1 to 4 carbon atoms.

The group R^2 is preferably selected from R^4, OQR^4, $C(O)_pR^4$, NR^6R^7, nitro, $C(O)NR^6R^7$, $OC(O)N(QR^6)R^7$, $NR^5C(O)_nR^6$, $NR^5CON(QR^6)R^7$, $NR^5CSN(QR^6)R^7$, $NR^5C(O)OR^6$ where Q, R^4, R^5, R^6 and R^7 are as defined above.

Preferably R^2 is selected from R^4, OQR^4, NR^6R^7 and $C(O)NR^6R^7$ where Q, R^4, R^5, R^6 and R^7 are as defined above.

A particularly preferred group R^2 is OR^4. In this case R^4 is suitably substituted alkyl, in particular substituted methyl, heterocyclyl or carbocyclyl. In particular, R^4 is substituted alkyl where the substitutent on the alkyl group is aryl in particular phenyl, which may itself be optionally substituted with one or more groups selected from alkyl such as C_{1-3} alkyl, halo such as chloro, alkylsulphonyl such as methylsulphonyl, alkoxy such as methoxy, aryl such as phenyl or aryloxy such as phenoxy.

A further preferred group R^2 is a group $NR^5C(O)OR^6$ where R^5 is hydrogen and R^6 is alkyl, in particular C_{1-6} alkyl, such as butyl or tert-butyl.

Particular examples of compounds of formula (I) are listed in Tables 1- 3 below.

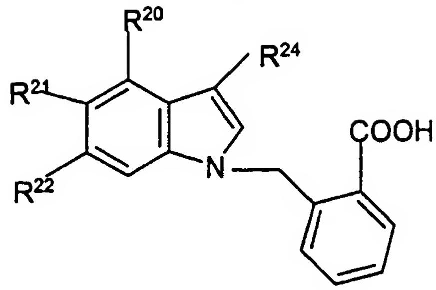
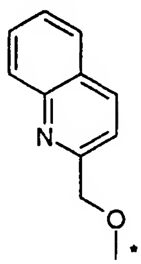
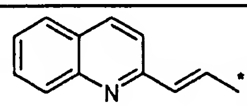
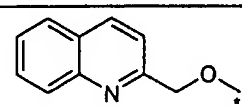
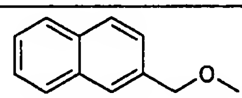
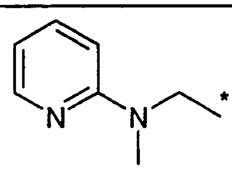
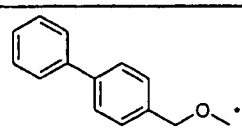
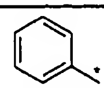
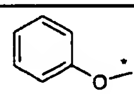
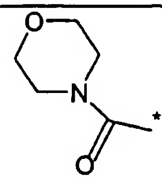
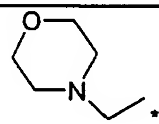
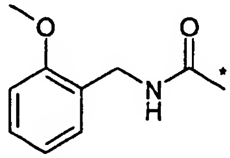
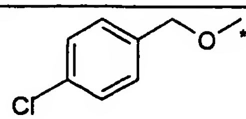
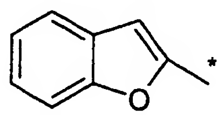
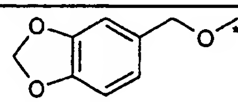
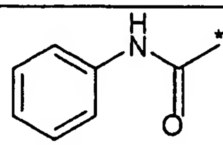
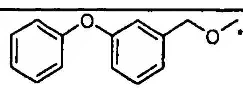
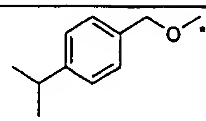
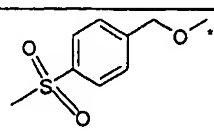
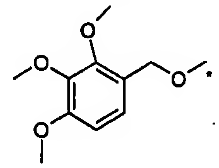
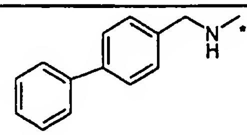
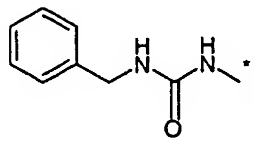
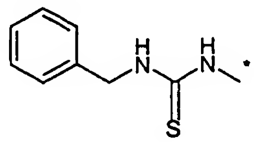
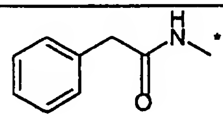
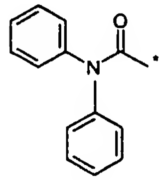
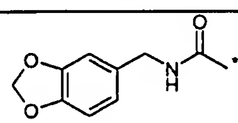
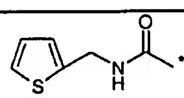
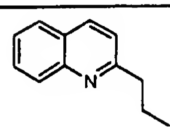
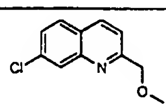
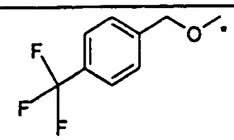
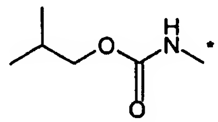
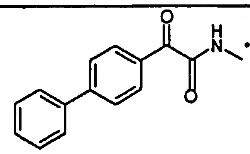
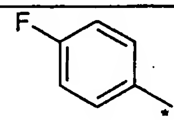
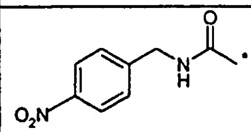
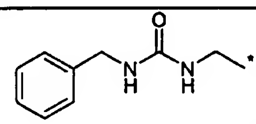
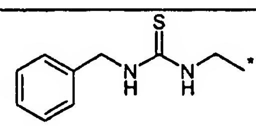
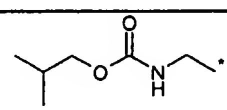
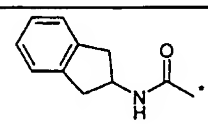
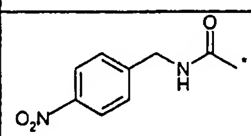
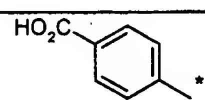


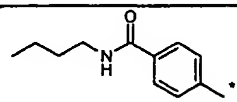
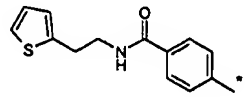
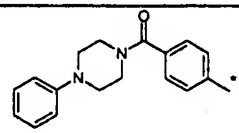
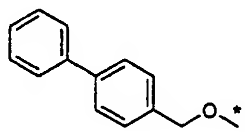
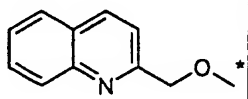
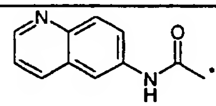
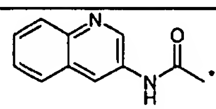
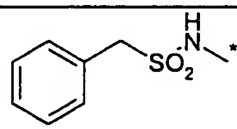
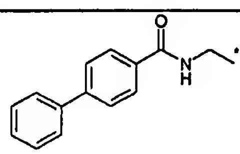
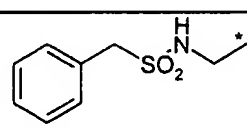
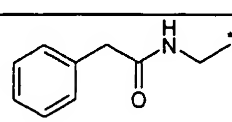
Table 1

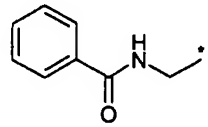
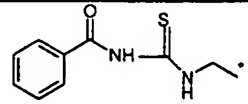
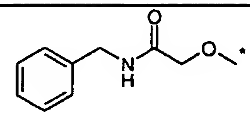
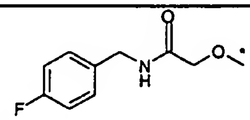
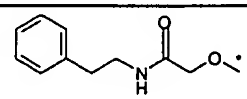
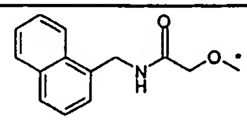
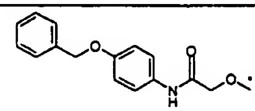
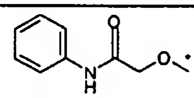
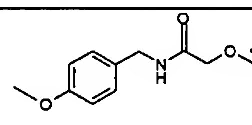
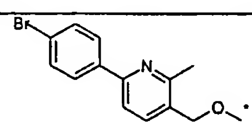
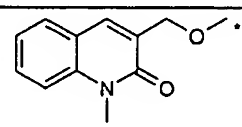
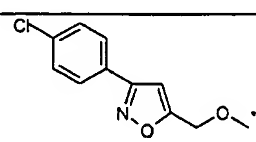
No	R^{20}	R^{21}	R^{22}	R^{24}
1		H	H	H
2	H		H	H
3	H	H		H
4	H		H	H
5	H		H	H
6	H		H	H
7	H		H	H
8	H		H	H

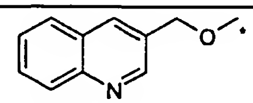
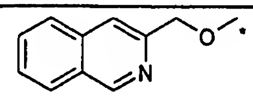
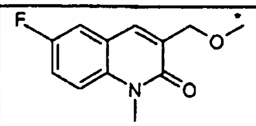
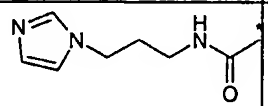
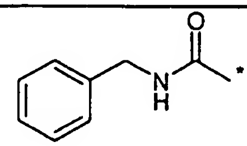
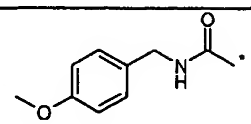
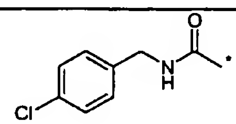
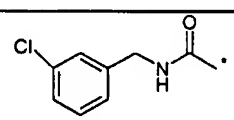
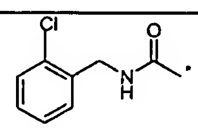
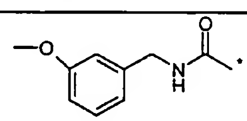
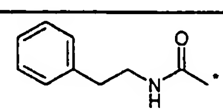
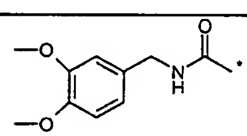
9	H		H	H
10	H		H	H
11	H	NO_2	H	H
12	H		H	H
13	H		H	H
14	H		H	H
15	H		H	H
16	H		H	H
17	H		H	H
18	H		H	H
19	H		H	H
20	H		H	H

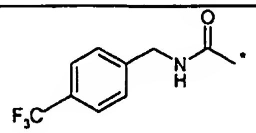
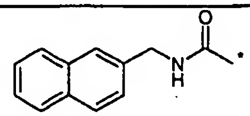
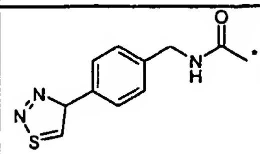
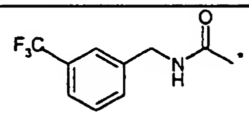
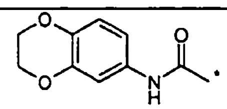
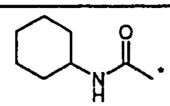
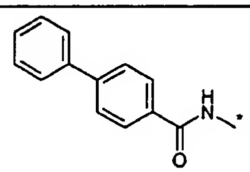
21	H		H	H
22	H		H	H
23	H		H	H
24	H		H	H
25	H		H	H
26	H	$CH_3(CH_2)_3NHC(O)$-	H	H
27	H		H	H
28	H		H	H
29	H		H	H
30	H	H		H
31		H	H	H

32	H		H	H
33	H		H	H
34	H		H	H
35	H		H	H
36	H		H	H
37	H		H	H
38	H		H	H
39	H		H	H
40	H		H	H
41	H		H	H
42	H		H	H

43	H		H	H
44	H		H	H
45	H		H	H
46	H		H	CH_3
47	H		H	CH_3
48	H		H	H
49	H	COOH	H	H
50	H		H	H
51	H		H	H
52	H		H	H
53	H		H	H
54	H		H	H

55	H		H	H
56	H		H	H
57	H		H	H
58	H		H	H
59	H		H	H
60	H		H	H
61	H		H	H
62	H		H	H
63	H		H	H
64	H		H	H
65	H		H	H
66	H		H	H

67	H		H	H
68	H		H	H
69	H		H	H
70	H		H	H
71	H		H	H
72	H		H	H
73	H		H	H
74	H		H	H
75	H		H	H
76	H		H	H
77	H		H	H
78	H		H	H

79	H		H	H
80	H		H	H
81	H		H	H
82	H		H	H
83	H		H	H
84	H		H	H
85	H		H	H

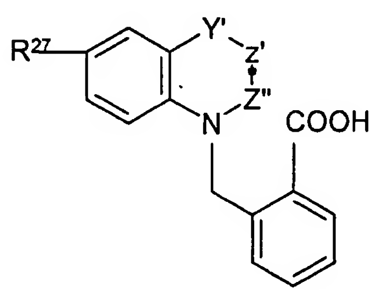
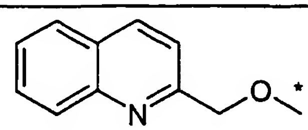
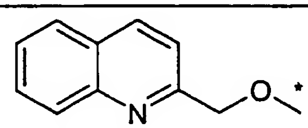
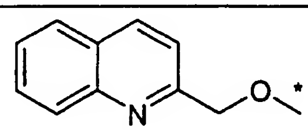


Table 2

No	R^{27}	Y'	Z'	Z"
100		CH_2	CH_2	CH_2
101		CH	CH	C(O)
102		CH_2	CH_2	C(O)

The use of certain compounds of formula (I) in any medical application has not been described before. Hence, in a further aspect the invention provides the use of these particular compounds as medicaments, and pharmaceutical compositions containing them.

Thus the invention provides compounds of formula (IA) which comprises a compound of formula (I) as defined above, where X is a bond or a group CH_2 or C(O); and -Y-Z- is selected from is selected from $-CR^{17}=CR^{18}-$, $-C(O)-CR^{17}=CR^{18}-$, $-CR^{17}=CR^{18}C(O)-$, $-CHR^{17}-CHR^{18}-C(O)-$, $-CHR^{17}-CHR^{18}-CHR^{19}-$, where R^{17}, R^{18} and R^{19} are independently selected from hydrogen or C_{1-3} alkyl such as methyl; provided that

(i) where the group of sub-formula (a) as defined above is a group of sub-formula (h) and R^{17} and R^{18} are hydrogen, R^2 is other than (2-ethyl-5,7-dimethyl-3H imidazo [4,5-b]pyridin-3-yl)methyl, or methyl substituted with an aromatic heterocyclic ring containing 2 or 3 nitrogen atoms;

(ii) where the group of sub-formula (a) as defined above is a group of sub-formula (g) as defined above and R^{17} and R^{18} are hydrogen, R^2 is other than a group $S(O)_qNR^6R^7$ where q is 2, R^6 is hydrogen and R^7 is 2-chlorophenyl; or

(iii) where the group of sub-formula (a) is a group of sub-formula (i) as defined above and R^{17} and R^{18} are hydrogen, either R^2 is other than halo, cyano, nitro, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, optionally substituted phenyl or a group OR^{14}, $NR^{14}R^{15}$ or SR^{14} where R^{14} and R^{15} are selected from hydrogen, C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl or optionally substituted phenyl, or m is other than 0.

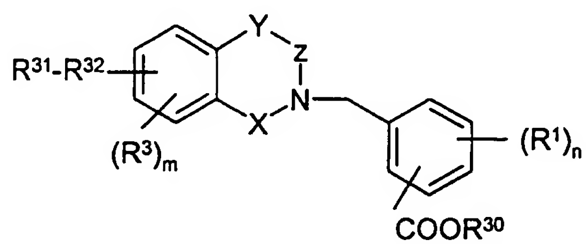
for use as a medicament, in particular for the activation of PPARγ and in the treatment of diabetes.

In addition, the invention provides a pharmaceutical composition comprising a compound of formula (IA) in combination with a pharmaceutically acceptable carrier.

Compounds of formula (IA) as defined above are novel and form a further aspect of the invention.

Preferred groups and moieties which are present in the compounds of formula (IA) are those preferred groups defined above in relation to formula (I).

Compounds of formula (I) are either known compounds or they may be prepared using conventional methods. In particular however, compounds of formula (I) may be prepared by reacting a compound of formula (III)



(III)

with a compound of formula (IV)

$$R^{34}\text{-}R^{33} \qquad \text{(IV)}$$

where X, Y, Z, R^3, R^1, n and m are as defined in relation to formula (I),

R^{30} is an ester protecting group, in particular an alkyl group,

one of R^{31} or R^{33} is a leaving group and the other is hydrogen or a group which reacts with and eliminates said leaving group,

R^{32} is a bond or is a precursor to R^2, and

R^{34} is a group R^2 as defined in relation to formula (I) or a part thereof, such that where R^{34}-R^{32} forms a group R^2;

and thereafter if necessary or desired carrying out one or more of the following steps:

(i) removing a protecting group R^{30}:

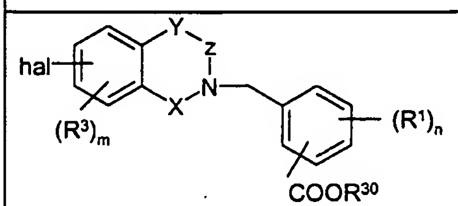
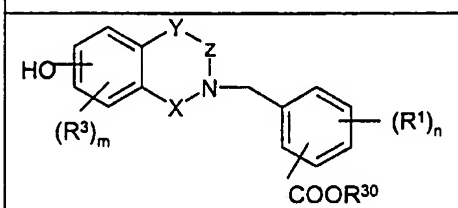
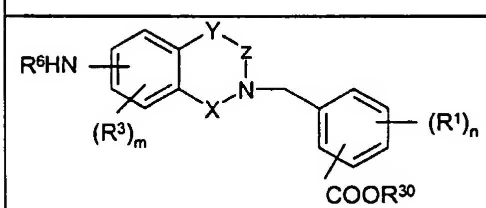
(ii) converting a group R^2 to a different such group.

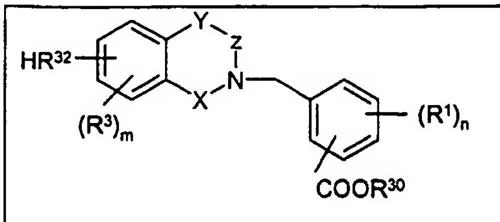
Suitable leaving groups for R^{31} or R^{33} include halogen, such as bromine, mesylate or tosylate. Other examples of leaving groups may comprise hydroxy, where for example this forms part of an acid group (e.g. in the case of R^{31}, where R^{32} comprises a carbonyl group) which

may be condensed, for example with amines of formula (IV) to form compounds where R^2 is an amide group. The other may comprise hydrogen, but other reactive groups such as boronic acid, which would react with and eliminate halo groups may also be employed. The reaction is suitably effected in a solvent such as an organic solvent and or water, in the presence of a base such as an alkali metal carbonate such as potassium carbonate. Catalysts such as palladium catalysts and elevated temperatures for example at the reflux temperature of the solvent, may be employed to assist the reaction.

Examples of groups R^{32} include functional type derivatives such as secondary amine groups $-NR^6-$, -O-, C(O), $S(O)_q$, $C(O)NR^6$, $OC(O)NR^6$, $NR^5C(O)_n$, NR^5CONR^6, NR^5CSNR^6, $NR^5C(O)O$, $N=CR^6$, $S(O)_qNR^6$or $NR^5S(O)_q$ where p, q and R^5 and R^6 are as defined above. Terminal groups such as R^4 and R^7 will then comprise the moiety R^{34} above. Examples of such reactions are illustrated hereinafter. Suitable combinations of compounds of formula (III) and (IV) can be summarised are illustrated in Table 3

Table 3

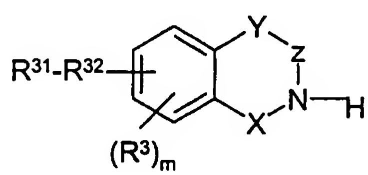
III	IV
	R^2-H
	R^4-hal
	R^7-hal where hal is a halogen atom such as bromine or chlorine

	R^{34}-hal where hal is a halogen atom such as bromine or chlorine

Deprotection to remove the group R^{30} can be carried out by conventional methods, for example by acidifying the compound using a mineral acid such as hydrochloric acid.

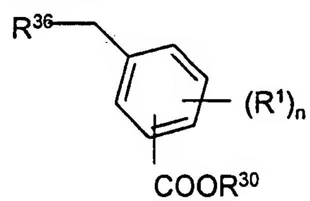
Optional step (ii) above can be carried out using various methods depending upon the nature of the R^2 groups involved and could be derived from the literature.

Compounds of formula (III) may be prepared by reacting a compound of formula (V)



(V)

where X, Y, Z, R^3, and m are as defined in relation to formula (I), and R^{31} and R^{32} are as defined in relation to formula (III), with a compound of formula (VI)

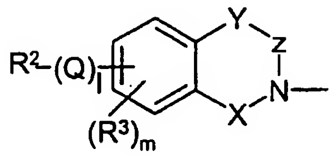


(VI)

where R^1 and n are as defined in relation to formula (I), R^{30} is as defined in relation to formula (III) and R^{36} is a leaving group.

Suitable leaving groups for R^{36} include those listed above for R^{31} or R^{33} and in particular is halo such as bromo. The reaction is suitably effected in an organic solvent such as butanone or dimethylformamide (DMF), in the presence of a base such as an alkali metal carbonate, for example potassium carbonate or an alkali metal hydride such as sodium hydride. Elevated temperatures, for example the reflux temperature of the solvent may be employed.

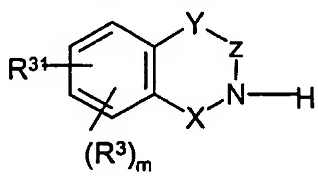
Alternatively, compounds of formula (I) may be prepared by reacting a compound of formula (VII)



(VII)

where X, Y, Z, R^2, R^3 and m are as defined in relation to formula (I), with a compound of formula (VI) as defined above, and thereafter if necessary or desired, carrying out optional steps (i) and (ii) above. Suitable reaction conditions will be similar to those described for the reaction between compound of formula (V) and (VI).

Compounds of formula (VII) may be prepared by reacting a compound of formula (VIII)



(VIII)

where X, Y, Z, R^3 and m are as defined in relation to formula (I) and R^{31} is as defined in relation to formula (III), which a compound of formula (IV) as defined above. Suitable reaction conditions include those listed above for the reaction between compounds of formula (III) and (IV).

Compounds of formulae (IV), (V), (VI) and (VIII) are either known compounds or they can be prepared from known compounds by conventional methods. Compounds of formula (V) where R^{31}-R^{32} is a complex moiety may be constructed in stages as would be understood by a chemist, and examples of such procedures are given hereinafter.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or acetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. In particular, compounds of formula (I) and compositions containing them will be used in the treatment of diabetes.

Thus in yet a further aspect, the invention provides a method of treating diabetes which comprises administering to a patient an effective amount of a compound of formula (I) as defined above.

The invention will now be particularly described by way of example.

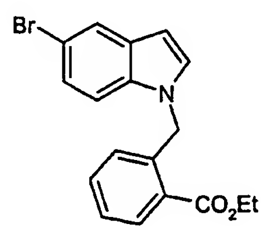
EXAMPLES

Example 1

Preparation of Compound 42 in Table 1

Step 1

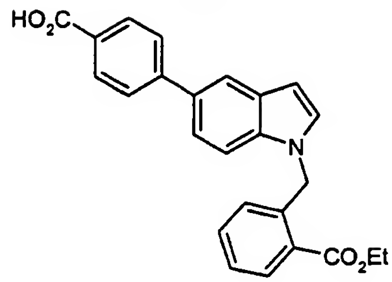
Preparation of 5-Bromo-1-(2-carboethoxybenzyl)indole



A mixture of 5-bromoindole (11.36 g, 58 mmol), ethyl 2-bromomethylbenzoate (73% pure, 23.4 g, 70 mmol) and powdered potassium carbonate (40 g, 0.29 mol) in 2-butanone (265 ml) was stirred under reflux for 40 hr. The cooled reaction mixture was filtered and the filter cake was washed well with 2-butanone. The filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate. This solution was washed with water, dried and evaporated. The crude product was chromatographed on Kieselgel 60, eluting with a gradient of 0-5% v/v ethyl acetate in isohexane. Fractions containing the required product by tlc were pooled, evaporated and the product was rechromatographed, eluting with a gradient of 10-25% v/v dichloromethane in isohexane. There was thus obtained 5-Bromo-1-(2-carboethoxybenzyl)indole (5.82 g) as an oil: NMR d (d_6-DMSO) 1.33 (3 H, t), 4.33 (4 H, q), 5.77 (2 H, s), 6.43 (1H, d), 6.52 (1 H, d), 7.17 (1 H, d), 7.28 (1 H, d), 7.39 (2 H, m), 7.47 (1 H, d), 7.76 (1 H, s), 7.92 (1 H, d); MS $[MH]^+$ 358/360.

Step 2

Preparation of 1-(2-Carboethoxybenzyl)-5-(4-carboxyphenyl)indole



A mixture of 5-bromo-1-(2-carboethoxybenzyl)indole (260 mg, 0.73 mmol) from Step 1, 4-carboxybenzeneboronic acid (145 mg, 0.87 mmol), potassium carbonate (361 mg, 2.6 mmol) and dichlorobis[tri(*o*-tolyl)phosphine]palladium(II) (17 mg, 0.02 mmol) in 1,2-dimethoxyethane (10 ml) and water (5 ml) was stirred for 1 hr at 100°C. The cooled reaction mixture was acidified with 2M hydrochloric acid to pH 1 and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated. The crude product was purified by chromatography on a 10g Isolute™ silica column, eluting with dichloromethane followed by 0.5% v/v ethanol in dichloromethane. There was thus obtained 1-(2-carboethoxybenzyl)-5-(4-carboxyphenyl)indole (144 mg): NMR d (d_6-DMSO) 1.33 (3 H, t), 4.33 (4 H, q), 5.80 (2 H, s), 6.49 (1 H, d), 6.61 (1 H, d), 7.43 (5 H, m), 7.79 (2 H, d), 7.96 (4 H, m); MS $[MH]^+$ 400.

Step 3

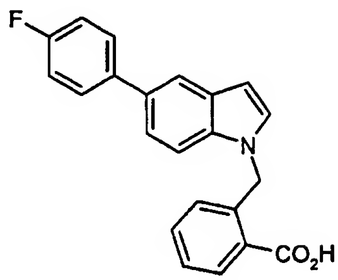
(1-(2-Carboxybenzyl)-5-(4-carboxyphenyl)indole) (Compound 42)

A mixture of 1-(2-carboethoxybenzyl)-5-(4-carboxyphenyl)indole (111 mg, 0.28 mmol) and 1M aqueous lithium hydroxide (830 µl, 0.83 mmol) in ethanol (10 ml) was stirred for 16 hr under reflux. A further portion of 1M lithium hydroxide (8.3 ml, 83 mmol) was added and stirring under reflux was continued for 3 hr, when tlc indicated that complete hydrolysis had occurred. The ethanol was evaporated and the aqueous residue was acidified with 2M hydrochloric acid to pH 1. The precipitated solid was filtered off, washed with water, vacuum dried and chromatographed on a 10 g Isolute™ silica column (supplied commercially by International Sorbent Technology), eluting with a gradient of 0-10% v/v methanol in dichloromethane. There was thus obtained 1-(2-Carboxybenzyl)-5-(4-carboxyphenyl)indole (54 mg): NMR d (d_6-DMSO) 5.90 (2 H, s), 6.54 (1 H, d), 6.68 (1 H, d), 7.48 (5 H, m), 7.85 (2 H, d), 8.03 (4 H, m); MS $[MH]^+$ 372.

Example 2

Preparation of Compound 35 in Table 1

(1-(2-Carboxybenzyl)-5-(4-fluorophenyl)indole)



By the method of Example 1 and using 4-fluorobenzeneboronic acid in place of 4-carboxybenzeneboronic acid, the starting material 5-bromo-1-(2-carboethoxybenzyl)indole was converted into 1-(2-carboxybenzyl)-5-(4-fluorophenyl)indole: NMR d (d_6-DMSO) 5.83 (2 H, s), 6.48 (1 H, d), 6.56 (1 H, d), 7.31 (6 H, m), 7.48 (1 H, d), 7.65 (2 H, m), 7.80 (1 H, s), 7.92 (1 H, m); MS $[MH]^+$ 346.

Example 3

Preparation of compound 15 in Table 1

1-(2-Carboxybenzyl)-5-(2-benzofuranyl)indole

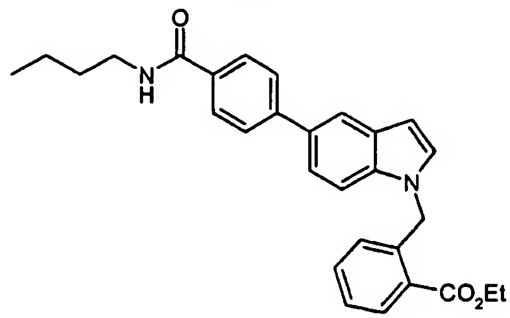
By the method of Example 1 and using benzofuran-2-boronic acid in place of 4-carboxybenzeneboronic acid, the starting material 5-bromo-1-(2-carboethoxybenzyl)indole was converted into 1-(2-carboxybenzyl)-5-(2-benzofuranyl)indole: NMR d (d_6-DMSO) 5.83 (2H, s), 6.48 (1H, d), 6.63 (1H, d), 7.43 (10H, m), 7.93 (1H, d), 8.16 (1H, s); MS $[MH]^+$ 368.

Example 4

Preparation of Compound 43 in Table 1

Step 1

Preparation of 5-(*N*-Butylcarboxamido)-1-(2-carboethoxybenzyl)indole



A mixture of 1-(2-carboethoxybenzyl)-5-(4-carboxyphenyl)indole (250 mg, 0.63 mmol) (Example 1 Step 2), n-butylamine (68 µl, 0.69 mmol), 1-hydroxybenzotriazole hydrate (105 mg, 0.69 mmol), N-methylmorpholine (76 µl, 0.69 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (132 mg, 0.69 mmol) in NN-dimethylformamide (10 ml) was stirred for 16 hr to give a clear solution. The solvent was evaporated and the residue was dissolved in dichloromethane (10 ml). This solution was washed sequentially with water, 1M aqueous citric acid, aqueous sodium bicarbonate and brine. The dried organic phase was evaporated to give 5-(*N*-butylcarboxamido)-1-(2-carboethoxybenzyl)indole (209 mg) as an orange gum: NMR d (d_6-DMSO) 0.89 (3 H, m), 1.33 (5 H, m), 1.51 (2 H, m), 3.27 (2 H, m), 4.36 (2 H, q), 5.80 (2 H, s), 6.49 (1 H, d), 6.60 (1 H, d), 7.41 (5 H, m), 7.73 (2 H, d), 7.91 (4 H ,m), 8.39 (1 H, t); MS $[MH]^+$ 455.

Step 2

5-(*N*-Butylcarboxamido)-1-(2-carboxybenzyl)indole (Compound 43)

A mixture of 5-(*N*-butylcarboxamido)-1-(2-carboethoxybenzyl)indole (176 mg, 0.39 mmol) and 1M aqueous lithium hydroxide (3.9 ml, 3.9 mmol) in ethanol (10 ml) was stirred for 60 hr to give a clear solution. The reaction mixture was evaporated to dryness and the residue was partitioned between dichloromethane (10 ml), methanol (1 ml) and water (5 ml) with acidification of the aqueous layer to pH 1 with 1M hydrochloric acid. The organic layer was filtered and evaporated to dyness to yield 5-(*N*-butylcarboxamido)-1-(2-carboxybenzyl)indole (111 mg) as a yellow solid: NMR d (d_6-DMSO) 0.89 (3 H, m), 1.33 (2 H, m), 1.51 (2 H, m), 3.27 (2 H, m), 5.83 (2 H, s), 6.47 (1 H, d), 6.60 (1 H, d), 7.41 (5 H, m), 7.84 (6 H, m), 8.39 (1 H, t); MS $[MH]^+$ 427.

]

Example 5

Preparation of Compound 44 in Table 1

1-(2-Carboxybenzyl)-5-{*N*-[2-(2-thienyl)ethyl]carboxamido}indole

By the method of Example 4 and using 2-(2-thienyl)ethylamine in place of n-butylamine, the starting material 1-(2-carboethoxybenzyl)-5-(4-carboxyphenyl)indole was converted into 1-(2-carboxybenzyl)-5-{*N*-[2-(2-thienyl)ethyl]carboxamido}indole: NMR d (d_6-DMSO) 3.07 (2 H, m), 3.51 (2 H, m), 5.83 (2 H, s), 6.48 (1 H, d), 6.60 (1 H, d), 6.93 (2 H, m), 7.40 (6 H, m), 7.83 (6 H, m), 8.60 (1 H, t); MS $[MH]^+$ 481.

Example 6

Preparation of Compound 45 in Table 1

1-(2-Carboxybenzyl)-5-{[(4-phenylpiperazino)carbonyl]phenyl}indole

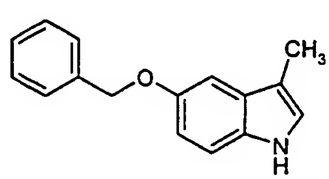
By the method of Example 4 and using 4-phenylpiperazine in place of n-butylamine, the starting material 1-(2-carboethoxybenzyl)-5-(4-carboxyphenyl)indole was converted into 1-(2-carboxybenzyl)-5-{[(4-phenylpiperazino)carbonyl]phenyl}indole: NMR d (d_6-DMSO) 3.14 (4 H, m), 3.65 (4 H, m), 5.83 (2 H, s), 6.49 (1 H, d), 6.60 (1 H, d), 6.80 (1 H, t), 6.94 (2 H, m), 7.21 (2 H, t), 7.43 (7 H, m), 7.73 (2 H, d), 7.93 (2 H, m); MS $[MH]^+$ 516.

Example 7

Preparation of Compound 47 in Table 1

Step 1

5-Benzyloxy-3-methylindole

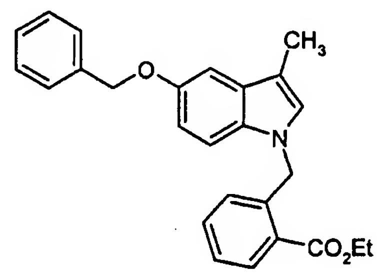


A solution of 5-benzyloxyindole-3-carboxaldehyde (3.78 g, 15.1 mmol) in anhydrous tetrahydrofuran (70 ml) was stirred during the dropwise addition of a 1.0M solution of lithium aluminium hydride in tetrahydrofuran (30 ml) at such a rate as to cause the solution to reflux gently. Stirring was continued for 3 hr whilst the solution cooled to ambient temperature. Ethyl acetate (10 ml) was cautiously added follows by water (50 ml). The mixture was filtered through

celite and the filter cake was washed well with ether. The filtrates were extracted with ether. The ether extracts were dried and evaporated to a brown gum which was chromatographed on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 40% v/v dichloromethane in isohexane. There was thus obtained the title compound (2.05 g): NMR δ ($CDCl_3$) 2.30 (3 H, s), 5.13 (3 H, s), 6.92 (1 H, dd), 6.93 (1 H, s), 7.13 (1 H, d), 7.24 (1 H, d), 7.30 (3 H, m), 7.47 (1 H, s), 7.50 (1 H, d), 7.75 (1 H, broad); MS $[MH]^+$ 238.

Step 2

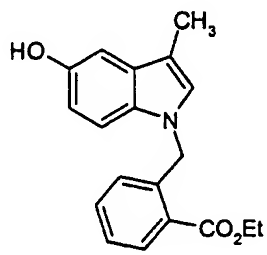
5-Benzyloxy-2-(2-carboethoxybenzyl)-3-methylindole



Sodium hydride (367 mg of a 60% dispersion in mineral oil, (9.2 mmol) was added in portions to a stirred solution of 5-Benzyloxy-3-methylindole (1.98 g, 8.35 mmol) in anhydrous N,N-dimethylformamide (30 ml). Stirring was continued for 30 min then a solution of ethyl 2-bromomethylbenzoate (2.54 g, 10.4 mmol) in N,N-dimethylformamide (5 ml) was added and the mixture was stirred for 16 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and evaporated to a gum which was purified by chromatography on Kieselgel 60, eluting with 40%v/v dichloromethane in isohexane to yield the title compound as a pale golden gum (2.24 g): NMR δ ($CDCl_3$) 1.42 (3 H, t), 2.54 (3 H, s), 4.41 (2 H, q), 5.13 (2 H, s), 6.53 (1 H, m),6.78 (1 H, s), 6.79 (1 H, m), 7.06 (1 H, d), 7.14 (1 H, d), 7.30 (5 H, m),7.50 (2 H, m), 8.03 (1 H, m); MS $[MH]^+$ 400.

Step 3

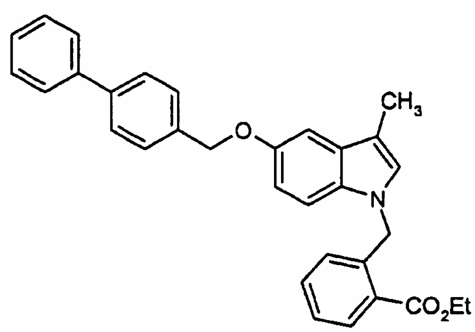
2-(2-Carboethoxybenzyl)-5-hydroxy-3-methylindole



Iodotrimethylsilane (185 μl, 1.3 mmol) was added to a stirred solution of 5-benzyloxy-2-(2-carboethoxybenzyl)-3-methylindole (399 mg, 1 mmol) in dichloromethane (3 ml). After 15 min further iodotrimethylsilane (185 μl) was added and after 5 min the reaction mixture was diluted with methanol (10 ml). The solvents were evaporated and the residue was dissolved in ether. The solution was washed with aqueous sodium metabisulphite, aqueous sodium bicarbonate, brine, dried and evaporated to a gum. The crude product was purified by chromatography on Kieselgel 60, eluting with dichloromethane to yield the title compound as a colourless gum (101 mg): NMR δ ($CDCl_3$) 1.42 (3 H, t), 2.30 (3 H, s), 4.39 (2 H, q), 4.50 (1 H, s), 5.65 (2 H, s),6.52 (1 H, m), 6.70 (1 H, m), 1H (1H, s), 6.99 (2 H, m), 7.30 (2 H, m), 8.02 (1 H, m); MS $[MH]^+$ 310.

Step 4

1-(2-Carboethoxybenzyl)-3-methyl-5-(4-phenylbenzyloxy)indole



A mixture of 2-(2-carboethoxybenzyl)-5-hydroxy-3-methylindole (95 mg, 0.31 mmol), 4-phenylbenzyl chloride (68 mg, 0.34 mmol) and potassium carbonate (47 mg, 0.34 mmol) in

anhydrous N,N-dimethylformamide (5 ml) was stirred at 80°C for 6.5 hr. The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic phase was washed with brine, dried and evaporated to a gum which was chromatographed on Kieselgel 60 eluting with 1:1 v/v dichloromethane/isohexane to yield the title compound as a gum (94 mg): NMR δ ($CDCl_3$) 1.43 (3 H, t), 2.32 (3 H, s), 4.40 (2 H, q), 5.18 (2 H, s), 5.68 (2 H, s), 6.55 (1 H, m), 6.90 (1 H, s), 6.92 (1 H, dd), 7.07 (1 H, d), 7.28 (2 H, m), 7.35 (1H, d), 7.47 (2 H, dd), 7.6 (6 H, m), 8.04(1 H, m); MS $[MH]^+$ 476.

Step 5

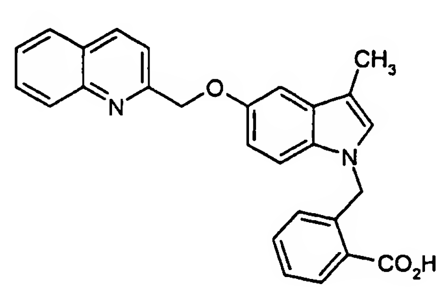
1-(2-Carboxybenzyl)-3-methyl-5-(4-phenylbenzyloxy)indole (Compound 46?)

A mixture of 1-(2-carboethoxybenzyl)-3-methyl-5-(4-phenylbenzyloxy)indole (84 mg, 0.18 mmol) and 1M aqueous lithium hydroxide (360 µl, 0.36.mmol) in ethanol was stirred for 16 hr. The reaction mixture was evaporated to dryness and the residue was partitioned between ether and water. The aqueous phase was acidified (2N HCl) to pH 1 and evaporated to dryness. The residue was chromatographed on a 5g C18(EC) Isolute™ column (supplied commercially by International Sorbent Technology) eluting with a gradient of 0-40% v/v acetonitrile in water. Fractions containing the pure title compound by HPLC were pooled and evaporated to yield an amorphous off-white solid (30 mg): NMR δ (d_6-DMSO) 2.23 (3 H, s), 5.15 (2 H, s), 5.67 (2 H, s), 6.44 (1 H, d), 6.80 (2 H, dd), 7.14 (3 H, m), 7.35 (3 H, m), 7.44 (1 H, d), 7.47 (1 H, d), 7.65 (4 H, m), 7.91 (1 H, m); MS $[MH]^+$ 448.

Example 8

Preparation of Compound 47 in Table 1

1-(2-Carboxybenzyl)-3-methyl-5-(2-quinolinylmethyloxy)indole



By the method of Example 1 and using 2-chloromethylquinoline hydrochloride in place of 4-phenylbenzyl chloride, 1-(2-carboxybenzyl)-3-methyl-5-(2-quinolinylmethyloxy)indole was prepared: NMR δ (d_6-DMSO) 2.20 (3 H, s), 5.36 (2 H, s), 5.66 (2 H, s), 6.44 (1 H, s), 6.95 (1 H, dd), 7.15 (3 H, m), 7.35 (2 H, m), 7.60 (1 H, dd), 7.70 (1 H, d), 7.78 (1 H, dd), 7.90 (1 H, d), 7.97 (1 H, d), 8.02 (1 H, d), 8.40 (1 H, d).

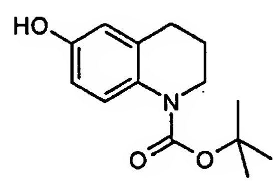
; MS $[MH]^+$ 423.

Example 9

Preparation of Compound 100 in Table 2

Step 1

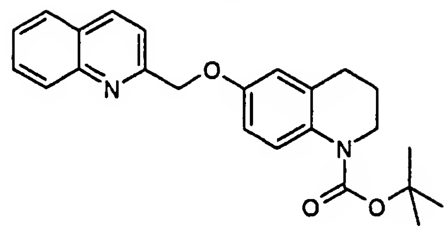
1-(*tert*-Butoxycarbonyl)-6-hydroxy-1,2,3,4-tetrahydroquinoline



A solution of 6-hydroxy-1,2,3,4-tetrahydroquinoline (J. Chem. Soc. Perkin Trans. 1, 1980, 1933-9) (1.0 g, 6.71 mmol) in 1N aqueous sodium hydroxide (8 ml) was stirred during the dropwise addition of a solution of di-*tert*-butyl dicarbonate (1.74 g, 8 mmol) in tert-butanol (8 ml) over 15 min. Stirring was continued for 60 hr and the reaction mixture was partitioned between ethyl acetate and water, with acidification of the aqueous phase with 2N hydrochloric acid to pH1. The organic phase was washed with brine, dried and evaporated to a brown oil. The crude product was chromatographed on Kieselgel 60, eluting with a gradient of 0-10% v/v ethyl acetate in dichloromethane to yield 1-(*tert*-Butoxycarbonyl)-6-hydroxy-1,2,3,4-tetrahydroquinoline as a pale yellow oil (845 mg): NMR δ ($CDCl_3$) 1.52 (9 H, s), 1.90 (2 H, m), 2.70 (2 H, dd), 3.65 (2H, dd), 5.32 (1 H, s), 6.55 (1 H, d), 6.60 (1 H, dd), 7.44 (1 H, d); MS $[MH]^+$ 250.

Step 2

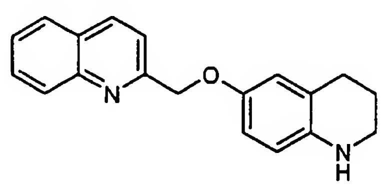
1-(*tert*-Butoxycarbonyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline



A mixture of 1-(*tert*-Butoxycarbonyl)-6-hydroxy-1,2,3,4-tetrahydroquinoline (825 mg, 3.31 mmol), 2-chloromethylquinoline hydrochloride (856 mg, 4.0 mmol) and powdered potassium carbonate (1.10 g, 8.0 mmol) in anhydrous N,N-dimethylformamide (8 ml) was stirred for 16 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried and evaporated to dryness. The crude product was chromatographed on Kieselgel 60, eluting with a gradient of 0-10% v/v ethyl acetate in dichloromethane to yield 1-(*tert*-butoxycarbonyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline as a pale yellow oil (560 mg): NMR δ ($CDCl_3$) 1.91 (2 H, m), 2.74 (2 H, dd), 3.68 (2 H, dd), 5.37 (2 H, s), 6.75 (1 H, d), 6.84 (1 H, dd), 7.55 (2 H, m), 7.58 (1 H, d), 7.75 (1 H, dd), 8.08 (1 H, d), 8.19 (1 H, d); MS $[MH]^+$ 391.

Step 3

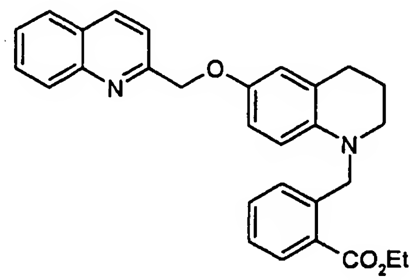
6-(2-Quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline Hydrochloride



1-(*tert*-Butoxycarbonyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline (550 mg, 1.41. mmol) was dissolved in ethyl acetate (5 ml) and the solution was treated with 4M hydrogen chloride in ethyl acetate (15 ml). After 60 hr the reaction mixture was evaporated to dryness to yield 6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline hydrochloride as a pale pink solid (478 mg): NMR δ (d_6-DMSO) 1.98 (2 H, m), 2.80 (2 H, m), 3.30 (2 H, m), 5.50 (2 H, s), 7.04 (2 H, m), 7.24 (1 H, d), 7.70 (1 H, dd), 7.78 (1 H, d), 7.90 (1 H, dd), 8.10 (1 H, d), 8.16 (1 H, d), 8.63 (1 H, d).

Step 4

1-(2-Carboethoxybenzyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline



A mixture of 6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline hydrochloride (468 mg, 1.43 mmol), ethyl 2-bromomethylbenzoate (696 mg of 76% strength, 2.17 mmol) and 2,6-lutidine (670 μl, 5.73 mmol) in anhydrous N,N-dimethylformamide (5 ml) was stirred for 2 hr at 95°C. The cooled reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried and evaporated to a dark brown oil. The oil was purified by chromatography on Kieselgel 60, eluting with a gradient of 33-100%v/v dichloromethane in isohexane followed by 0-8% v/v ethyl acetate in dichloromethane to yield 1-(2-carboethoxybenzyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline as a brown gum (179 mg): NMR δ ($CDCl_3$) 1.40 (3 H, t), 2.02 (2 H, m), 2.80 (2 H, dd), 3.30 (2 H, dd), 4.36 (2 H, q), 4.77 (2 H, s), 5.26 (2 H, s), 6.23 (1 H, d), 6.63 (1 H, dd), 6.76 (1 H, d), 7.28 (1 H, m), 7.42 (1 H, m), 7.52 (1 H, m), 7.70 (2 H, m), 7.80 (1 H, d), 8.00 (1 H, d), 8.17 (1 H, d), 8.30 (1 H, dd); MS $[MH]^+$ 453.

Step 5

1-(2-Carboxybenzyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline (Compound 100)

A mixture of 1-(2-carboethoxybenzyl)-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline (179 mg, 0.4 mmol) and 1M aqueous lithium hydroxide (4.0 ml, 4.0 mmol) in ethanol was stirred for 16 hr to give a clear solution. The reaction mixture was evaporated to dryness and the residue was dissolved in warm water (10 ml). The solution was acidified with 2N hydrochloric acid and then adjusted to pH 2 by the addition of powdered sodium bicarbonate. The pale buff precipitate was filtered off, washed with water and vacuum dried to yield the desired compound (62 mg): NMR δ (d_6-DMSO) 1.92 (2H, m), 2.75 (2 H, m), 3.30 (2 H, m), 4.68 (2 H, s), 5.18 (2 H, s), 6.12

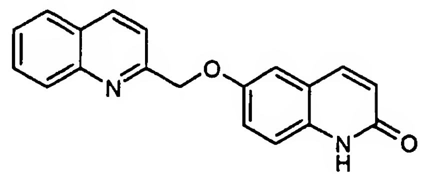
(1 H, d), 6.60 (1 H, dd), 6.62 (1 H, d), 7.28 (1 H, d), 7.33 (1 H, d), 7.45 (1 H, dd), 7.56 (1 H, d), 7.63 (1 H, d), 7.75 (1 H, m), 7.86 (1 H, d), 7.95 (2 H, m), 8.36 (1 H, d); MS $[MH]^+$ 425.

Example 10

Preparation of Compound 101 in Table 2

Step 1

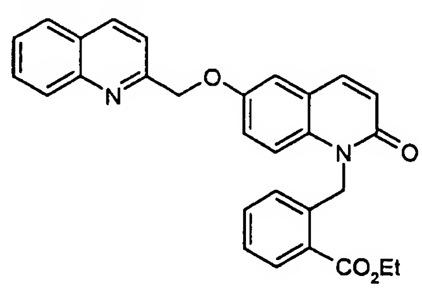
2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline



A mixture of 2,3-dihydro-6-hydroxy-2-oxoquinoline (Eur. J. Med. Chem., 1985, 20, 121-5) (2.58 g, 16 mmol), 2-chloromethylquinolin hydrochloride (3.76 g, 17.6 mmol) and powdered potassium carbonate (4.42 g, 32 mmol) in anhydrous N,N-dimethylformamide (24 ml) was stirred at 90°C for 6.5 hr. The cooled reaction mixture was poured into water. The precipitated solid was filtered off, washed with water, air dried and recrystallised from ethanol to yield 2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline (1.71 g): NMR δ (d_6-DMSO) 5.38 (2 H, s), 6.45 (1 H, d), 7.28 (2 H, m), 7.33 (1 H, d), 7.60 (1 H, dd), 7.68 (1 H, d), 7.98 (1 H, d), 8.02 (1 H, d), 8.40 1 H, d).

Step 2

1-(2-Carboethoxybenzyl)-2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline



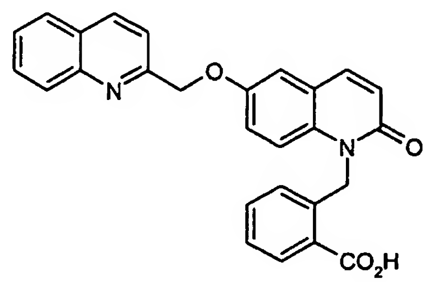
2,3-Dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline (800 mg, 2.65 mmol) was added in portions to a stirred suspension of sodium hydride (116 mg of 60% oil dispersion, 2.9 mmol) in anhydrous N,N-dimethyformamide (5 ml). When effervescence ceased a solution of ethyl 2-

bromomethylbenzoate (1.12 g, 76% strength, 3.5 mmol) in N,N-dimethylformamide (2 ml) was added.

The reaction mixture was stirred for 16 hr and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried and evaporated. Chromatography of the crude product on Kieselgel 60, eluting with a gradient of 0-6% ethanol in dichloromethane, afforded 1-(2-carboethoxybenzyl)-2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline (528 mg) as a brown gum: NMR δ ($CDCl_3$) 5.40 (2 H, s), 5.95 (2 H, s), 6.75 (1 H, d), 6.80 (1 H, d), 7.05 (1 H, d), 7.15 (2 H, m), 7.30 (3 H, m), 7.55 (1 H, dd), 7.64 (1 H, d), 7.68 (1 H, d), 7.75 (1 H, dd), 7.83 (1 H, d), 8.08 (1 H, d), 8.18 (1 H, d); MS $[MH]^+$ 465.

Step 3

1-(2-Carboxybenzyl)-2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline



A mixture of 1-(2-carboethoxybenzyl)-2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline (500 mg, 1.08 mmol) and 1M aqueous lithium hydroxide (10.8 ml, 10.8 mmol) in ethanol (20 ml) was stirred for 16 hr to give a clear solution. The reaction mixture was evaporated to dryness and the residue was dissolved in water (10 ml). The solution was acidified with 2N hydrochloric acid to pH 1. The resulting precipitate was filtered off, washed with water and vacuum dried to yield 1-(2-carboxybenzyl)-2,3-dihydro-2-oxo-6-(2-quinolinylmethyloxy)quinoline (433 mg): NMR δ (d_6-DMSO) 5.39 (2 H, s), 5.80 (2 H, s), 6.55 (1 H, d), 6.71 (1 H, d), 7.10 (1 H, d), 7.25 (1 H, dd), 7.35 (2 H, m), 7.50 (1 H, d), 7.60 (1 H, dd), 7.68 (1H, d), 7.78 (1 H, dd), 8.00 (4 H, m), 8.40 (1 H, d); MS $[MH]^+$ 437.

Example 11

Preparation of Compound 102 in Table 2

(1-(2-Carboxybenzyl)-2-oxo-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline)

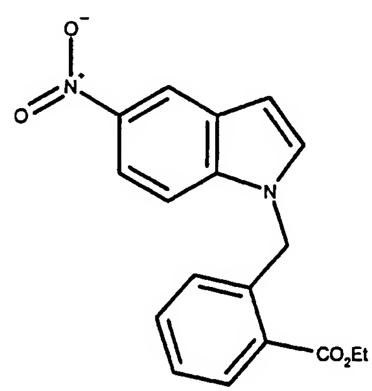
Using the method of Example 10 and using 6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline (Chem. Ber., 1927, 60, 858) in place of 2,3-dihydro-6-hydroxy-2-oxoquinoline, was prepared 1-(2-carboxybenzyl)-2-oxo-6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydroquinoline: NMR δ (d_6-DMSO) 2.68 (2 H, dd), 2.96 (2 H, dd), 5.35 (2 H, s), 5.38 (2 H, s), 6.58 (1 H, d), 6.80 (1 H, dd), 6.98 (1 H, d), 7.04 (1 H, d), 7.33 (1 H, dd), 7.43 (1 H, dd), 7.65 (1 H, dd), 7.72 (1 H, d), 7.83 (1 H, dd), 7.95 (1 H, d), 8.05 (2 H, m), 8.52 (1 H, d); MS $[MH]^+$ 439.

Example 12

Preparation of Compound 24 in Table 1

Step 1

1-(2-Carboethoxybenzyl)-5-nitroindole

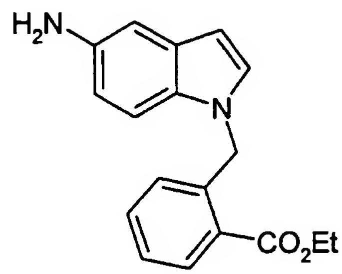


A mixture of 5-nitroindole (3.0 g, 18.5 mmol), ethyl 2-bromomethylbenzoate (5.0g, slight excess), potassium carbonate (10.0g, 72mmol),and potassium iodide (1 crystal), in N,N-dimethylformamide (50ml) were stirred together at room temperature over the weekend. After pouring into water the mixture was extracted with ethyl acetate. The combined extracts were dried (magnesium sulphate) and evaporated to give an oil. This was columned on Merck 7734 silica using a gradient of ethyl acetate and hexane to give 3.75g of the product:NMR d (d_6-

DMSO) 1.3 (3 H, t), 4.32 (2 H, q),5.86 (1 H, s), 6.5 (1 H, d), 6.82 (1 H, d), 7.35-7.5 (2 H, m), 7.55 (1 H, d), 7.65 (1 H, d), 7.95 (2 H, m) 8.6 (1H, d); MS (MH)+ 325.

Step 2

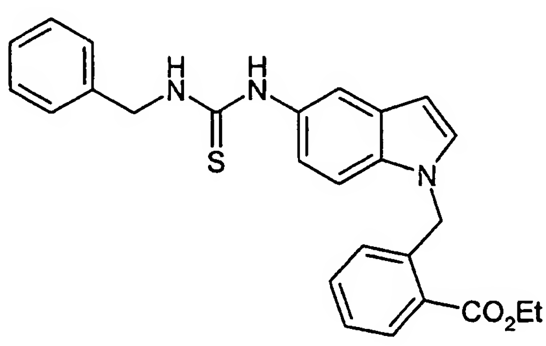
1-(2-Carbethoxybenzyl)-5-aminoindole



1-(2-Carboethoxybenzyl)-5-nitroindole (500 mg, 15.4mmol), was stirred with 10% Pd/C (50mg), in methylene chloride (20ml), at room temperature under hydrogen at one atmosphere. After the hydrogen uptake had ceased, the mixture was filtered through celite and evaporated to give the crude product as an oil (450 mg). This was used without further purification : NMR d (d_6-DMSO) 1.32 (3 H,t), 4.38 (2 H ,q), 4.5 (1H, s (broad)), 5.64 (2 H , s), 6.21 (1 H, d), 6.48 (2 H, d), 6.74 (1 H, s), 6.95 (1 H, s), 7.22 (1 H, s), 7.4 (2 H, m),7.93 (1 H, d); MS $(MH)^+$ 295 .

Step 3

1-(2-Carboethoxybenzyl)-5-(N (N'-benzyl)thioureido)indole



Benzylisothiocyanate (0.135ml 1mmol) in methylene chloride (0.5ml) was added at room temperature to a solution of 1-(2-carbethoxybenzyl)-5-aminoindole in methylene chloride (2ml).The mixture was stirred at room temperature overnight, evaporated to dryness and the

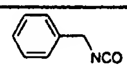
residue was chromatographed on Merck 7734 silica using a gradient of ethyl acetate and hexane to give the product as a solid : NMR d (d_6- DMSO) 1.36 (3 H, t), 4.35 (2 H, q), 4.72 (2 H, d), 5.79 (2 H, s), 6.5 (2 H, m), 6.97 (1 H, d), 7.19-7.54 (10 H, m), 7.82-7.98 (2 H, m), 9.5 (1 H, s); MS $(MH)^+$ 444.

Step 4 (Compound 24)

A mixture of 1-(2-carboethoxybenzyl)-5-(N (N'-benzyl) thioureido)indole (200 mg, 0.45mmol) and lithium hydroxide (200 mg, 4.8mmol) in dioxane (5 ml) and water (2 ml) were stirred together at room temperature for 7hr. The reaction mixture was evaporated to dryness and the residue was dissolved in water and acidified with 1.0N hydrochloric acid to give a precipitate. The solid was filtered off, and washed well with water. After drying under vacuum at room temperature an amorphous solid was obtained (160 mg): NMR d (d_6 -DMSO) 4.72 (2 H,d), 5.8 (2 H,s), 6.48 (1 H,d), 6.52 (1H,s), 6.95 (1H,d), 7.18-7.4 (8 H,m), 7.5 (2 H,m), 7.9 (2 H,m), 9.5 (1 H s), 13.21 (1H,s); MS $(MH)^+$ 416

Example 13

Using a method analogous to that described in Example 12, the following compounds were prepared:

Compound number	Alkylating Agent used in step 3	MS (MH)+	NMR d (d_6- DMSO)
23		400	4.27 (2 H, d), 5.72 (2 H, s), 6.3 (3 H, m), 6.99 (1 H, d), 7.1-7.42 (9 H, m), 7.68 (1 H, s), 7.9 (1 H, d),8.3 (1 H, s), 13.2 (1 H, b)

Example 14

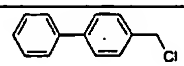
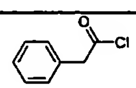
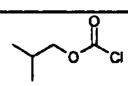
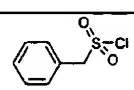
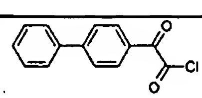
Preparation of Compound 85 in Table 2

4-Biphenylcarbonyl chloride (174mg 0.8mmol) was added to a solution of 1-(2-carbethoxybenzyl)-5-aminoindole (247mg 0.8mmol), prepared as described in Example 12 step 2, and triethylamine (0.12ml 0.86mmol) in dichloromethane (4ml) After stirring overnight at room temperature the mixture was evaporated and columned on Merck 7734 silica using a

gradient of ethyl acetate and hexane to give the desired product (220mg) : NMR d (d_6- DMSO) 1.35 (3 H, t), 4.36 (2 H, q), 5.75 (2 H, s), 6.4 (1 H, d), 6.52 (1 H, d), 7.22-8.11(16 H, m), 10.15 (1 H, s); MS $(MH)^+$ 475.

Example 15

Using a method analogous to that described in Example 14, the following compounds were prepared:

Compd. number	Alkylating Agent used instead of 4-Biphenyl-carbonyl chloride	MS (MH)+	NMR d (d_6- DMSO)
22		433	4.4 (2 H, s), 5.7 (2 H, s), 6.35 (2 H, m), 6.78-7.75 (16 H, m), 7.92 (1 H, d)
25		385	3.6 (2 H, s),5.74 (2 H, s), 6.34 (1 H, m), 6.43 (1 H, d), 7.12-7.48 (10 H, m), 7.92 (2 H, m), 10.0 (1 H, s), 13.15 (1 H, b)
33		367	0.9 (6 H, d),1.9 (3.86 (2 H, d), 5.76 (2 H, s),6.35 (1 H, d), 6.42 (1 H, d), 7.02-7.42 (5 H, m), 7.7 (1 H, s), 7.92 (1 H, m), 9.32 (1 H, s), 13.18 (1 H, s)
51		420	4.3 (2 H, s), 5.76 (2 H, s), 6.48 (2 H, d), 6.98 (1 H d), 7.2-7.5 (10 H, m), 7.98 (1 H, m), 9.45 (1 H, s).
34		475	5.98 (2 H, s), 6.39 (1 H, d), 6.55 (1 H, d), 7.22-8.2 (16 H, m), 10.8 (1 H, s), 12.9 (1 H, b)

Example 16

Preparation of Compound 11 in Table 1

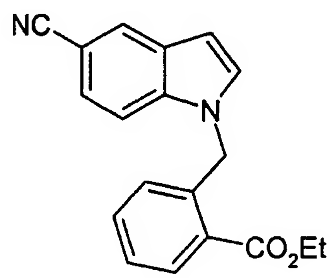
1-(2-Carboethoxybenzyl)-5-nitroindole (200mg 0.62mmol), 1.0N sodium hydroxide (1ml), and ethyl alcohol (5ml) were stirred together at 70^0 C for 2 hours. The mixture was cooled and then evaporated to dryness. The residue was dissolved in water and acidified with 1.0N hydrochloric acid solution to give a precipitate. The product was obtained after filtering off, washing well with water and vacuum drying.(143mg) : NMR d (d_6- DMSO) 5.9 (2 H, s), 6.45 (1 H, dd), 6.8 (1 H, d), 7.39 (2 H, m), 7.55 (1 H, d), 7.68 (1 H, d), 7.95 (2 H, m), 8.6 (1 H, s) 13.2 (1 H, s(broad))); MS $(MH)^+$297.

Example 17

Preparation of Compound 52 in Table 1

Step 1

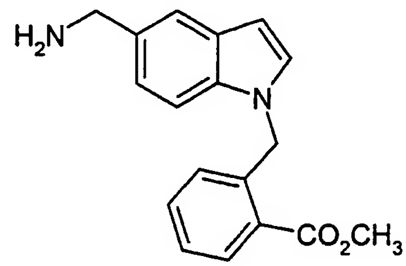
1-(2-Carboethoxybenzyl)-5-cyanoindole.



Sodium hydride (62 mg of60% suspension in oil , 1.55mmol) was added to a solution of 5-cyanoindole (200 mg, 1.4mmol) in N,N dimethylformamide. After evolution of the hydrogen had ceased , ethyl 2-bromomethylbenzoate (408 mg, 1.7mmol) was added and the mixture was stirred at room temperature overnight. After pouring into water and extracting with ethyl acetate, the combined extracts were dried over magnesium sulphate, filtered, and the filtrate was evaporated to leave an oil. The oil was chromatographed on Merck 7734 silica using a gradient of ethyl acetate and hexane to give the product as an oil (290 mg) : NMR d (d_6- DMSO) 1.32 (3 H, t), 4.32 (2 H, q), 5.85 (2 H, s), 6.46 (1 H, d), 6.7 (1 H, d), 7.38-7.98 (6 H, m), 8.13 (1 H, s) MS $(MH)^+$ 305.

Step 2

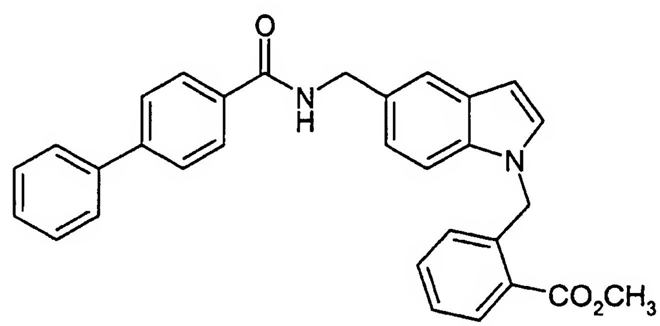
5-Methylamino-1-(2-carbomethoxybenzyl)indole.



1-(2-Carboethoxybenzyl)-5-cyanoindole (300 mg, 0.98 mmol) was dissolved in methyl alcohol (10ml) saturated with ammonia. This solution was hydrogenated at 50^0 C and 50 atmospheres pressure overnight. After filtering through celite and evaporating an oil was isolated (230mg) .This was used crude without any further purification: NMR d (CDCl3 and D2O) 3.93 (3 H, s), 4.15 (2 H, s) 5.77 (2 H, s), 6.42 (1 H, m) 6.58 (1 H, d) 7.1-7.4 (5 H, m), 7.65 (1 H, s) 8.1 (1 H, m). MS $(MH-NH_3)^+$ 278

Step 3

5-(Methylamino(N-biphenyl))-1-(2-carbomethoxybenzyl)indole.



4-Phenylbenzoyl chloride (152mg 0.7mmol) in methlene chloride was added to a mixture of 5-methylamino-1-(2-carbomethoxybenzyl)indole (200mg 0.68mmol) and triethylamine (0.1ml 0.72mmol) in methylene chloride at room temperature. After stirring overnight at room temperature the mixture was evaporated to dryness and the residue was chromatographed on Merck 7734 silica using a gradient of ethyl acetate and hexane to give the product (150mg):

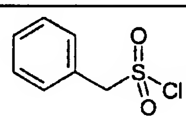
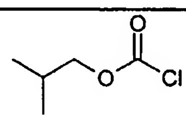
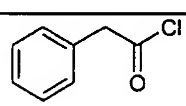
NMR d (d_6- DMSO) 3.9 (3 H, s), 4.5 (2 H, d), 5.76 (2 H, s), 6.35 (1 H, d), 6.5 (1 H, d), 7.04-8.06 (16 H, m), 9.05 (1 H, t); MS $(MH)^+$ 475

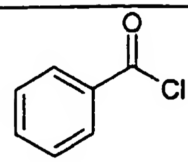
Step 4 (Compound 52)

A mixture of 5-(methylamino(N-biphenyl))-1-(2-carbomethoxybenzyl)indole (140 mg 0.295 mmol) and lithium hydroxide (24.8 mg 0.59mmol) in dioxane (5ml) and water (2ml) were stirred together at room temperature overnight. The reaction mixture was evaporated to dryness and the residue was dissolved in water and acidified with 1.0N hydrochloric acid to give a precipitate. The solid was filtered off, and washed well with water. After drying under vacuum at room temperature an amorphous solid was obtained (102 mg) : NMR d (d_6- DMSO) 4.55 (2 H, d), 5.79 (2 H, s), 6.35 (1 H, d), 6.5 (1 H, d), 7.04-8.06 (16 H, m), 9.05 (1 H, t); MS $(MH)^+$ 461

Example 18

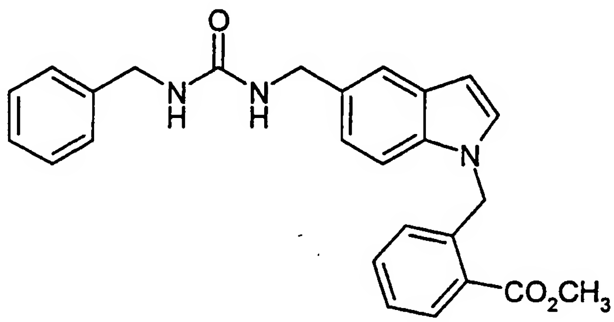
Using a method analogous to that described in Example 17, the following compounds were prepared.

Compound number	Alkylating Agent used in step 3	MS (MH)+	NMR d (d_6- DMSO)
53		435	4.15 (2 H, d), 4.24 (2 H, s), 5.79 (2 H, s), 6.35 (1 H, m), 6.5 (1 H, d), 7.04 (1 H, d), 7.2-7.58 (11 H, m), 7.92 (1 H, m), 13.3 (1 H, s)
39		381	0.95 (6 H, d), 1.86 (1 H, m), 3.79 (2 H, d), 4.28 (2 H, d)5.85 (2 H, s), 6.4 (1 H, d), 6.55 (1 H, d), 7.05 (1 H, d), 7.29 (1 H, d), 7.35-7.72 (5 H, m)8.0 (1 H, m), 13.2 (1 H, s)
54		399	3.45 (2 H, s), 4.32 (2 H, d), 5.78 (2 H, s), 6.32 (1 H, m), 6.45 (1 H, d), 6.98 (1 H, d), 7.15-7.48 (10 H, m), 7.95 (1 H, m), 8.45 (1 H, t), 13.2 (1 H, s

55		385	4.55 (2 H, d), 5.8 (2 H, s), 6.34 (1 H, m), 6.48 (1 H, d), 7.05 (1 H, d),7.28-7.56 (8 H, m), 7.95 (3 H, m), 9.0 (1 H, t), 13.2 (1 H, b).

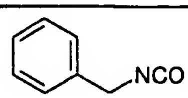
Example 19

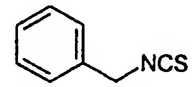
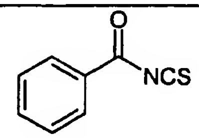
Preparation of Compound 37 in Table 1



5-Methylamino-1-(2-carbomethoxybenzyl)indole.(200mg 0.68mmol) and benzylisocyanate (93.1mg 0.7mmol) were stirred together in methylene chloride (3ml) at room temperature overnight. The mixture was evaporated and then columned on Merck 7734 silica using a gradient of ethyl acetate and hexane to give the product (100mg)): NMR d (d_6- DMSO) 3.9 (3 H, s), 4.26 (4 H, dd), 5.75 (2 H, s), 6.34 (3 H, m), 6.48 (1 H, d), 6.95 (1 H d), 7.12-7.49 (10 H, m), 7.91 (1 H, m) MS $(MH)^+$ 428

Using similar methodology but with a different alkylating agent, the following compounds were prepared.

Compd. number	Alkylating Agent	MS (MH)+	NMR d (d_6- DMSO)
37		414	4.26 (4 H, dd), 5.78 (2 H, s), 6.32 (3 H, m), 6.48 (1 H, d), 7.0 (1 H d), 7.14-7.5 (10 H, m),7.92 (1 H, m),13.2 (1 H, s).

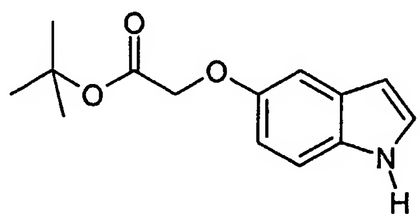
38		430	4.7 (4 H, s(broad)), 5.8 (2 H, s), 6.32 (1 H, m), 6.49 (1 H d), 7.02 (1 H, d), 7.12-8.01 (13 H, m) 13.25 (1 H, b).
56		444	4.65 (2 H, s (broad)), 5.8 (2 H, s), 6.3 (1 H, d), 6.48 (1 H, d), 6.85-8.0 (14 H, m),13.18 (1 H, s)

Example 20

Preparation of Compound 57 in Table 1

Step 1

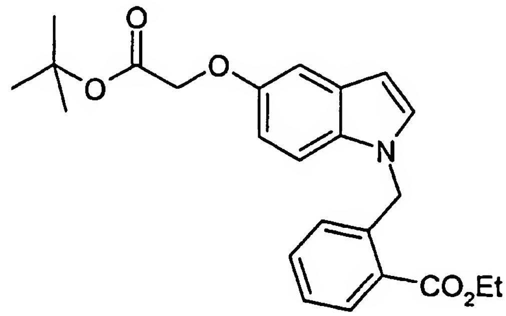
t-Butyl ester of indole-5-oxyacetic acid.



Sodium hydride (1.3g (60% suspension in oil) 32.5mmol) was added to a solution of 5-hydroxyindole (4.0g 30mmol) in N,N-dimethylformamide .After the hydrogen evolution had ceased t-butylbromoacetate (5.4ml 33.4mmol)was added and the mixture was stirred at room temperature overnight. The mixture was poured into water extracted with ether and the combined extracts were washed with water and dried over magnesium sulphate. After filtering the filtrate was evaporated to give an oil. Columning on Merck silica 7734 using a gradient of ethyl acetate and hexane gave the product (5.75g): NMR d (d_6- DMSO) 1.4 (9 H, s), 4.58 (2 H, s) 6.3 (1 H, s) 6.72 (1 H, d), 6.96 (1 H, s), 7.28 (2 H, m), MS $(MH)^+$ 248.

Step 2

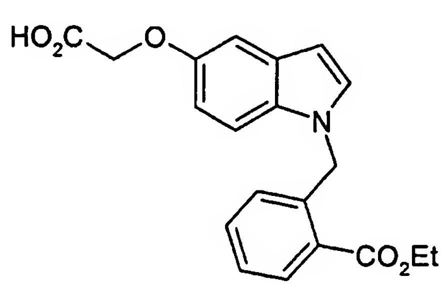
t-Butyl ester of 1-(2-carboethoxybenzyl)-indole-5-oxyacetic acid



Sodium hydride (920mg(60% suspension in oil) 23mmol) was added to a solution of the t-Butyl ester of indole-5-oxyacetic acid (5.7g 23mmol) in NN dimetylformamide (50ml). When the hydrogen evolution had ceased, ethyl 2-bromomethylbenzoate (5.6g 23mmol) was added. The mixture was stirred at room temperature overnight, and then poured into water. After extracting with ether the combined extracts were washed with water and dried over magnesium sulphate. The mixture was filtered and the filtrate was evaporated to leave an oil. Chromatography on Merck 7734 silica using a gradient elutant of ethyl acetate and hexane yielded the pure product.(4.0g)): NMR d (d_6- DMSO) 1.33 (3 H, t), 1.42 (9 H, s), 4.34 (2 H, q), 4.6 (2 H, s),5.72 (2 H, s), 6.4 (2 H, m),6.72 (1 H, d),7.0 (1 H, s), 7.19 (1 H, d), 7.37 (3 H, m), 7.9 (1 H, d) MS $(MH)^+$ 410.

Step 3

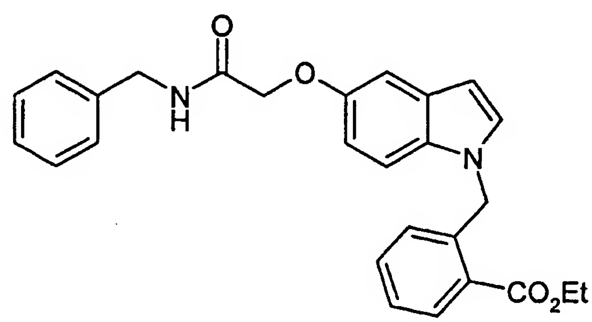
1-(2-carboethoxybenzyl)-indole-5-oxyacetic acid.



Trimethylsilyl triflate (0.89ml 4.9mmol) was added at room temperature to a stirred solution of the t-butyl ester of 1-(2-carboethoxybenzyl)-indole-5-oxyacetic acid (550mg 1.35mmol) and triethylamine (0.75ml 5.4mmol) in dry dioxane(5ml) The mixture was heated at 60^0 C for three hours . After evaporation the residue was partitioned between water and ether . The combined ether extracts were washed with water brine and then dried over magnesium sulphate. The product was obtained as a crude oil after filtering and evaporating the filtrate. Columning on Merck 7734 silica using a gradient of ethyl acetate and hexane yielded the pure product (350mg) : NMR d (d_6- DMSO) 1.28 (3 H, t), 4.3 (2 H, q), 4.55 (2 H, s), 5.68 (2 H, s), 6.33 (2 H, m), 6.65 (1 H, d), 6.96 (1 H, s), 7.13 (1 H, d), 7.32 (3 H, m), 7.83 (1 H, d), 12.79 (1 H, b) MS $(MH)^+$ 354.

Step 4

1-(2-Carboethoxybenyl)-5-((N- benzyl) oxyacetamido)indole.



Benzylamine (0.16ml 1.46mmol), 1-(2-carboethoxybenzyl)-indole-5-oxyacetic acid, (338mg 0.96mmol), and O-(7-azabenzotriazol-1-yl)-NNN',N'-tetramethyluroniumhexafluorophosphate [HATU] (550mg 1.45mmol) were stirred together at room temperature in NN dimethylformamide (3ml). Diisopropylethylamine (0.67ml 3.85mmol) was added and the mixture was stirred at room temperature for 1 hour. After pouring into 1.0N hydrochloric acid, the mixture was extracted with ether. The combined extracts were washed with 1.0N hydrochloric acid,water and brine. The extract was dried over magnesium sulphate and evaporated to give the crude product. Chromatography on Merck 7734 silica using a gradient of ethyl acetate and hexane gave the pure product (295mg): NMR d (d_6- DMSO) 1.34 (3 H, t), 4.35 (4 H, m), 4.52 (2 H, s), 5.78 (2 H, s), 6.4 (1 H, d), 6.44 (1 H, d), 6.8 (1 H, dd), 7.08-7.45 (10 H, m),7.9 (1 H, m), 8.6 (1 H, t) MS $(MH)^+$ 443

Step 5

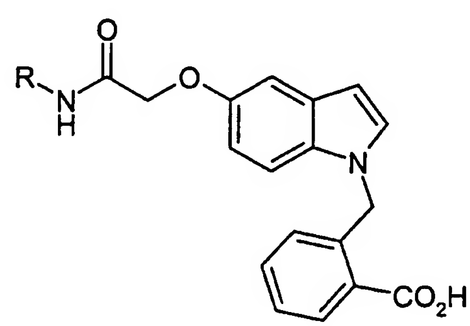
Compound 57

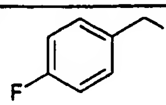
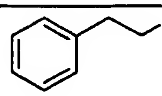
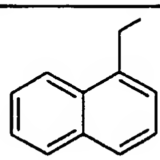
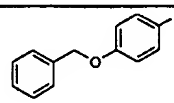
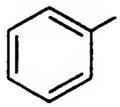
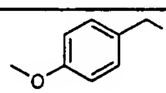
A mixture of 1-(2-carboethoxybenyl)-5-((N- benzyl) oxyacetamido)indole (280mg 0.65mmol) and lithium hydroxide (136mg, 3.24mmol) in dioxane (3ml) and water (1ml) were stirred together at room temperature overnight. The reaction mixture was evaporated to dryness and the residue was dissolved in water and acidified with 1.0N hydrochloric acid to give a precipitate. The precipitate was filtered off, and washed well with water. After drying under vacuum at room temperature an amorphous solid was obtained (175mg): NMR d (d_6- DMSO) 4.35 (2 H, d), 4.52 (2 H, s), 5.76 (2 H, s), 6.39 (1 H, d), 6.45 (1 H, d), 6.82 (1 H, dd), 7.1-7.48 (10 H, m),7.95 (1 H, m),8.6 (1 H, t), 13.18 (1 H, b) MS $(MH)^+$ 415.

Example 21

Using a method analogous to that described in Example 20, the following compounds were prepared.

General Structure



Comp. No.	R	MS (MH)+	NMR d (d_6- DMSO)
58		433	4.3 (2 H, d), 4.52 (2 H, s), 5.75 (2 H, s), 6.35 (1 H, m), 6.43 (1 H, d), 6.89 (1 H, dd), 7.0-7.48 (9 H, m), 7.91 (1 H, m), 8.65 (1 H, t)
59		429	2.75 (2 H, t), 3.35 (2 H, under water peak), 4.4 (2 H, s), 5.75 (2 H, s), 6.35 (1 H, m), 6.42 (1 H, d), 6.78 (1 H, dd), 7.07 (1 H, d), 7.12-7.46 (9 H, m), 7.92 (1 H, m), 8.1 (1 H, t), 13.15 (1 H, s)
60		465	4.62 (2 H, s), 4.88 (2 H, d), 5.82 (2 H, s), 6.45 (2 H, m), 6.85 (1 H, dd), 7.15 (1 H, d), 7.25 (1 H, d), 7.32-7.64 (7 H, m), 7.88 (1 H, t), 7.98 (2 H, m), 8.18 (1 H, m), 8.7 (1 H, t), 13.25 (1 H, s)
61		507	4.6 (2 H, s), 5.08 (2 H, s), 6.75 (2 H, s), 6.35 (1 H, d), 6.42 (1 H, d), 6.8 (15 H, m), 7.93 (1 H, m), 9.9 (1 H, s)
62		401	4.72 (2 H, s), 5.8 (2 H, s), 6.42 (1 H, d), 6.5 (1 H d), 6.85-7.52 (9 H, m), 7.72 (2 H, d), 8.0 (1 H, m), 10.05 (1 H s), 13.15 (1 H s)
63		445	3.7 (3 H, s), 4.28 (2 H, d), 4.46 (2 H, s), 5.75 (2 H, s), 6.35 (1 H, m), 6.41 (1 H, d)6.72-7.48 (10 H, m), 7.91 (1 H, m), 8.52 (1 H, t), 13.2 (1 H, s).

Example 22

Preparation of Compound No 10 in Table 1

Step 1

Methyl-1-(2-carboethoxybenzyl)-indole-5-oxyacetate)

Methyl-1-(2-carboethoxybenzyl)-indole-5-oxyacetate) was made using an analogous route to that used above for the preparation of the t-butyl ester of 1-(2-carboethoxybenzyl)-indole-5-oxyacetic acid. : NMR d (d_6- DMSO) 1.19 (3 H, t), 1.32 (3 H, t), 4.0 (2 H, q), 4.33 (2 H, q), 4.7 (2 H, s), 5.7 (2 H, s), 6.42 (2 H, m), 6.73 (1 H, dd), 7.03 (1 H, d), 7.18 (1 H, d), 7.37 (3 H, m), 7.9 (1 H, dd) MS $(MH)^+$ 382.

Step 2

Compound 10

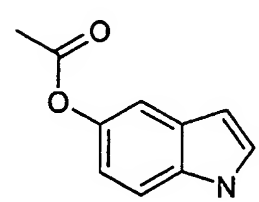
Ethyl-1-(2-carboethoxybenzyl)-indole-5-oxyacetate (125mg 0.33mmol),1.0N sodium hydroxide (2ml) and ethyl alcohol (10ml) were heated together at 70^0 C for 2 hours. The reaction was cooled and the solvent was evaporated off. The residue was dissolved in water and acidified with 1.0 N hydrochloric acid. The precipitate was filtered off,washed well with water and dried under vacuum at room temperature . (80mg) : NMR d (d_6- DMSO) 4.6 (2 H, s), 5.75 (2 H, s), 6.4 (2 H, m), 6.7 (1 H, m), 7.03 (1 H, s), 7.17 (1 H, d), 7.33 (3 H, m), 7.9 (1 H, d) ; MS $(MH)^+$ 326.

Example 23

Preparation of Compound 32 in Table 1

Step 1

5-acetoxy-indole



To a solution of 5-hydroxy-indole (12.00g, 90.12mmol) in pyridine (300ml) was added acetic anhydride (9.35ml, 99.13mmol) and dimethylaminopyridine (100mg, *cat*). The reaction was stirred for three hours at room temperature when pyridine was evaporated to yield a residue which was partitioned between water and ethyl acetate. The aqueous layer was washed a further three timed with ethyl acetate and the organic layers collected, washed with water, dried over magnesium sulfate and evaporated to yield the desired product (15.82g) as an off-white solid. δ

(CDCl$_3$, 300MHz) 2.30 (3 H, s), 6.49-6.53 (1 H, m), 6.87-6.92 (1 H, m), 7.12-7.16 (1 H, m), 7.33-7.338 (2 H, m), 8.08-8.8.28 (1 H, s), MS [MH]+176.

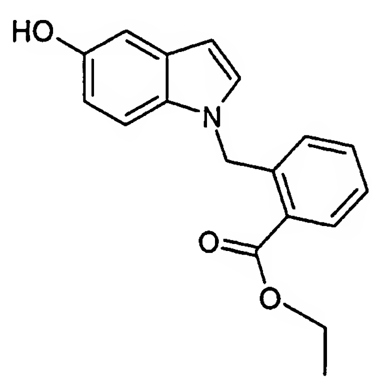
Step 2

1-(2-Carboethoxybenzyl)-5-acetoxy-indole

Sodium hydride (3,98g of a 60% dispersion on oil, 90.4mmol) was added to a stirring solution of 5-acetyl-indole (15.82g, 90.40mmol) in N, N-dimethylformamide (300ml) and 2-Carboethoxybenzylbromide (18.90ml, 108.48mmol) was added. The reaction was stirred at room temperature for 16 hours and subsequently partitioned between water and ethyl acetate. The aqueous layer was washed a further three timed with ethyl acetate and the organic layers collected, washed twice with water, dried over magnesium sulfate and evaporated to yield the desired product (30g) δ (CDCl$_3$, 300MHz) 1.37-1.42 (3 H, t), 1.63 (3 H,. s), 4.35-4.42 (2 H, q), 5.54 (2 H, s), 6.56-6.57 (1 H, d), 7.04-7.13 (2 H, m), 7.37-7.41 (2 H, m), 7.52-7.58 (1 H, t), 7.78-7.81 (1 H, d), 8.02-8.06 (1 H, d), 8.32-8.36 (1 H, d): MS [MH]+338.

Step 3

1-(2-Carboethoxybenzyl)-5-hydroxy-indole



A mixture of 1-(2-Carboethoxybenzyl)-5-acetoxy-indole (26.67mg, 79.14mmol) and sodium ethoxide (9.23mg 21% solution on ethanol, 135.60mmol) was dissolved in ethanol (1250ml) and heated to 60°C for 1.5 hours, The reaction was cooled to room temperature and partitioned between water and ethyl acetate. The aqueous layer was washed a further three times with ethyl acetate and the organic layers collected, dried over magnesium sulfate and evaporated to yield the desired product which was purified by chromatography on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 20% v/v ethyl acetate in isohexane. Thus was obtained the desired

product as an off-white solid (13.79g): δ (d_6-DMSO, 300MHz) 2.29 (3 H, s), 6.52-6.54 (1 H, m), 6.88-6.94 (1 H, m), 7.18-7.20 (1 H, m), 7.34-7.38 (2 H, m), 8.10-8.25 (1 H, s); MS $[MH]^+$176.

Step 4

1-(2-Carboethoxybenzyl)-5-(4-trifluoromethylbenzyloxy)-indole

A mixture of 1-(2-Carboethoxybenzyl)-5-hydroxy-indole (3.35g, 1.17mmol), potassium carbonate (0.57g, 4.09mmol) and 4-trifluoromethyl-benzyl-bromide (0.31g, 1.29mmol) in dimethylformamide (3ml) was heated to 100°C for 48 hours. The reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was further extracted three times with ethyl acetate and the collected organic layers dried over magnesium sulfate and evaporated.

Step 4a

In an alternative experiment, step 1 was repeated as described above, except 1.5 molar equivalents of sodium hydride (60% dispersion in oil) were used instead of potassium carbonate, and the reaction stirred at room temperature for 16 hours, not 100°C for 48 hours.

Step 5

1-(2-Carboxybenzyl)-5-(4-trifluoromethylbenzyloxy)-indole (Compound 32)

1-(2-Carboethoxybenzyl)-5-(4-trifluoromethylbenzyloxy)-indole (from step 1) was dissolved in 1,4-dioxane (5ml) at 60°C, 2M aqueous sodium hydroxide (5ml, 10mmol) was added and the mixture stirred for 16 hours. The 1,4-dioxane was removed and the aqueous residue acidified with 1M hydrochloric acid. The resultant solid precipitate was filtered off washed with toluene and dried to an amorphous off-white solid (12.5mg) 1-(2-Carboxybenzyl)-5-(4-trifluoromethylbenzyloxy)-indole:

δ (d_6-DMSO, 300MHz) 5.42 (2 H, s), 5.49 (2 H, s), 6.41-6.42 (1 H, d), 6.83-6.87 (1 H, d), 7.08 (1 H, s), 7.30-7.34 (3 H, m), 7.41-7.43 (1 H, t), 7.48-7.49 (1 H, d), 7.56-7.59 (1 H, t), 7.66-7.68 (3 H, m), 7.90-7.93 (1 H, d), 13.07 (1 H, s): MS $[MH]^+$ 426.

Example 24

Using a method analogous to that described in Example 23,the following compounds were prepared.

Compd No.	Mass ion	NMR data
19	$[MH]^+$ 400	δ (d_6-DMSO, 300MHz) 1.13-1.15 (6 H, d), 2.79-2.84 (1 H, m), 5.31 (2 H, s), 5.42 (2 H, s), 6.36-6.37 (1 H, d), 6.80-6.84 (1 H, q), 7.05-7.06 (1 H, d), 7.09-7.17 (4 H, m), 7.34-7.44 (3 H, m), 7.55-7.60 (1 H, t), 7.66-7.69 (1 H, d), 7.90-7.93 (1 H, d), 13.05 (1 H, s).
21	$[MH]^+$ 448	δ (d_6-DMSO, 300MHz) 3.59 (3 H, s), 3.68 (6 H, s), 5.26 (2 H, s), 5.42 (2 H, s), 6.36-6.37 (1 H, d), 6.58 (2 H, s), 6.82-6.85 (1 H, d), 7.05 (1 H, s), 7.39-7.47 (3 H, m), 7.54-7.60 (1 H, t), 7.67-69 (1 H, d), 7.90-7.93 (1 H, d), 13.02 (1 H, s).
14	$[MH]^+$ 392	δ (d_6-DMSO, 300MHz) 3.35 (2 H, s), 3.43 (2 H, s), 6.36-6.37 (1 H, d), 6.79-6.83 (1 H, q), 7.07-7.08 (1 H, d), 7.15-7.17 (2 H, d), 7.23-7.40 (4 H, m), 7.43-7.44 (1 H, d), 7.48-7.52 (1 H, t), 7.64-7.66 (1 H, d), 7.88-7.80 (1 H, d).
18	$[MH]^+$ 450	δ (d_6-DMSO, 300MHz) 5.37 (2 H, s), 5.42 (2 H, s), 6.36-6.37 (1 H, d), 6.81-6.85 (3 H, m), 6.90-6.95 (3 H, t), 7.05-7.15 (2 H, m) 7.27-7.45 (6 H, m), 7.55-7.60 (1 H, t), 7.68-7.70 (1 H, d), 7.90-7.93 (1 H, d), 13.06 (1 H, s).
16	$[MH]^+$ 402	δ (d_6-DMSO, 300MHz) 5.25(2 H, s), 5.42 (2 H, s), 5.95 (2 H, s), 6.35-6.36 (1 H, d), 6.71-6.84 (3 H, m), 7.04-7.05 (1 H, d), 7.12-7.21 (1 H, m), 7.36-7.44 (3 H, m), 7.54-7.59 (1 H, t), 7.66-7.69 (1H, d), 7.90-7.92 (1 H, d), 13.12 (1 H, s).

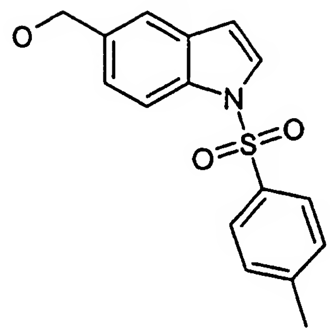
20	$[MH]^+$ 436	δ (d_6-DMSO, 300MHz) 3.16 (3 H, s), 5.42 (2 H, s), 5.51 (2 H, s), 6.42-6.43 (1 H, d), 6.78-6.86 (1 H, m), 7.08-7.09 (1 H, d), 7.20-7.70 (8 H, m), 7.84-7.90 (2 H, m), 13.04 (1 H, s).
6	$[MH]^+$ 434	δ (d_6-DMSO, 300MHz) 5.15 (2 H, s), 5.78 (2 H, s), 6.39-6.43 (2 H, m), 6.78-6.84 (1 H, m), 7.17-7.72 (14 H, m), 7.84-7.91 (1 H, m).
3	$[MH]^+$ 409	δ (d_6-DMSO, 300MHz)5.35 (2 H, s), 5.80 (2 H, s), 6.34-6.35 (1 H, d), 6.48-6.53 (1 H, d), 6.83-6.88 (1 H, q), 6.97-7.01 (1 H, t), 7.05-7.13 (1 H, t), 7.16 (1 H, s), 7.31-7.36 (1 H, d), 7.47-7.48 (1 H, d), 7.58-7.67 (2 H, m), 7.70-7.73 (1 H, d), 7.78-7.83 (1 H, t), 7.97-8.08 (2 H, m), 8.38-8.40 (1 H, d).
4	$[MH]^+$ 408	δ (d_6-DMSO, 300MHz) 5.31 (2 H, s), 5.37 (2 H, s), 6.27-6.29 (1 H, d), 6.70-6.75 (1 H, q), 6.90-6.98 (1 H, d), 7.04-7.08 (2 H, m), 7.09-7.13 (1 H, q), 7.16-7.23 (1 H, t), 7.28-7.31 (2 H, m), 7.34-7.40 (1 H, m), 7.42-7.46 (3 H, m), 7.58-7.66 (2 H, m), 7.85-7.89 (1 H, q).
8	$[MH]^+$ 344	δ (d_6-DMSO, 300MHz) 5.78 (2 H, s), 6.48-6.53 (2 H, m), 6.82-6.84 (1 H, q), 6.90-6.92 (2 H, d), 7.03-7.08 (1 H, t), 7.23-7.24 (1 H, d), 7.33-7.52 (6 H, m), 7.97-7.99 (1 H, d).
64	$[MH]^+$ 529	δ (d_6-DMSO, 300MHz) 2.37 (3 H, s), 5.27 (2H, s), 5.43 (2 H, s), 6.35-6.36 (1 H, d), 6.86-6.89 (1 H, q), 7.05-7.06 (1 H, d), 7.40-7.59 (7 H, m), 7.67-7.69 (1 H, d), 7.86-7.92 (4 H, m).

65	$[MH]^+$ 439	δ (d_6-DMSO, 300MHz) 3.67 (2 H, s), 5.28 (2 H, s), 5.43 (2 H, s), 6.39-6.40 (1 H, d), 6.82-6.84 (1 H, q), 7.08-7.09 (1 H, d), 7.19-7.23 (1 H, t), 7.36-7.46 (4 H, m), 7.53-7.60 (5 H, m), 7.67-7.70 (1 H, d), 7.89-7.93 (1 H, d).
66	$[MH]^+$ 459	δ (d_6-DMSO, 300MHz) 5.45 (2 H, s), 5.63 (2 H, s), 6.40-6.41 (1 H, d), 6.86-6.91 (2 H, m), 7.06-7.07 (1 H, d), 7.30-7.34 (1 H, t), 7.41-7.62 (6 H, m), 7.81-7.84 (3 H, m).
67	$[MH]^+$ 409	δ (d_6-DMSO, 300MHz) 5.42 (2 H, s), 5.63 (2 H, s), 6.43-6.44 (1 H, d), 6.81-6.85 (1 H, q), 7.08-7.09 (1 H, d), 7.38-7.47 (2 H, m), 7.54-7.68 (4 H, m),7.74-7.97 (1 H, t), 7.77-8.03 (3 H, m), 8.21 (1 H, s), 8.90 (1 H, s).
68	$[MH]^+$ 409	δ (d_6-DMSO, 300MHz) 5.42 (2 H, s), 5.60 (2 H, s), 6.41-6.42 (1 H, d) 6.79-6.83 (1 H, m), 7.08-7.09 (1 H, d), 7.38-7.72 (8 H, m), 7.74-7.92 (2 H, m), 8.10-8.12 (1 H, d), 9.30 (1 H, d).
69	$[MH]^+$ 457	δ (d_6-DMSO, 300MHz) 3.67 (3 H, s), 5.28 (2 H, s), 5.43 (2 H, s), 6.40-6.41 (1 H, d), 6.81-6.85 (1 H, q), 7.09-7.10 (1 H, d), 7.31-7.60 (8 H, m), 7.67-7.69 (1 H, d), 7.90-7.93 (1 H, d).

Example 25

Preparation of Compound No. 5 in Table 1

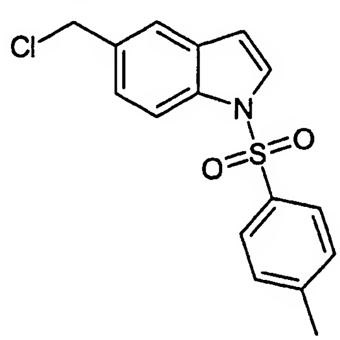
Step 1



A solution of 1-(*p*-toluenesulfonyl)-5-carbomethoxy-indole (13.88g, 42.18mmol) in tetrahydrofuran (100ml) was slowly added to a stirring 1M solution of lithium aluminium hydroxide at 0°C under an argon atmosphere. The temperature of the reaction was controlled below 5°C. The reaction was stirred at 0°C for 15 minutes and was subsequently quenched by dropwise addition of a saturated sodium sulfate solution at 0°C. A white precipitate formed, which was filtered off and washed with tetrahydrofuran. The filtrate was dried over magnesium sulfate and evaporated to yield a yellow oil. This was purified by chromatography on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 25% v/v ethyl acetate in isohexane. There was thus obtained the title compound (9.00g) as a light yellow glassy oil: δ (CDCl3, 300MHz) 2.34 (3 H, s), 4.71-4.72 (2 H, d), 6.62-6.63 (1 H, d), 7.18-7.20 (2 H, d), 7.29-7.31 (1 H, q), 7.55-7.56 (2 H, d), 7.72-7.74 (2 H, d), 7.98-8.00 (1 H, d): MS $[MH]^{-}$300.

Step 2

1-(*p*-toluenesulfonyl)-5-methylchloro-indole

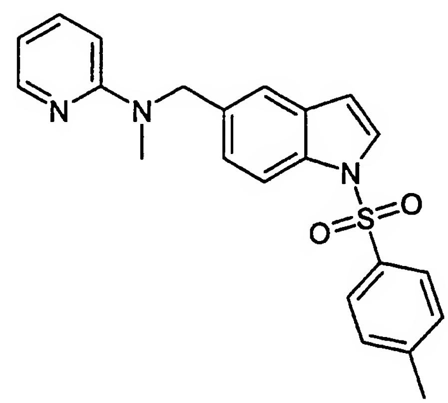


1-(*p*-toluenesulfonyl)-5-methylhydroxy-indole (9.00g, 30mmol) was dissolved in N,N-dimethylformamide (90ml). Carbontetrachloride (18.50g, 120mmol) and triphenylphosphine (9.04g, 35mmol) were added and the reaction was left to stir for 60 hours at room temperature.

Subsequently, the reaction was partitioned between ice water and ethyl acetate. The aqueous phase was further extracted three times with ethyl acetate and the collected organic layers were washed twice with water and once with a saturated sodium chloride solution, dried over magnesium sulfate and evaporated. The oily residue was purified by chromatography on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 50% v/v dichloromethane in isohexane. There was thus obtained the title compound (7.02g) as a white powder. δ (CDCl3, 300MHz) 2.32 (3 H, s), 4.68 (2 H, s), 6.62-6.63 (1 H, d), 7.19-7.24 (2 H, m), 7.32-7.34 (1 H, q), 7.58 (1 H, s), 7.60-7.61 (1 H, s), 7.74-7.76 (2 H, d), 7.94-7.96 (1 H, d): MS $[MH]^+$ 320.

Step 3

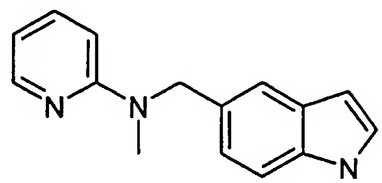
1-(*p*-toluenesulfonyl)-5-methyl-(N-methylamino)-pyridine-indole



1-(*p*-toluenesulfonyl)-5-methylchloro-indole (2.50g, 7.82 mmol) was dissolved in dimethylformamide (100ml) and potassiumiodide (1.56g, 9.38mmol), potassium carbonate (3.88g, 28.14mmol) and N-methylamino-pyridine (1.01g, 9.38mmol) were added. The reaction was heated to 60°C for 16 hours. Subsequently, the reaction was filtered and cooled to room temperature. The filtrate was partitioned between water and diethyl ether and the aqueous layer was extracted a further three times with diethyl ether. The collected organic layers were dried over magnesium sulfate and evaporated. The oily residue was purified by chromatography on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 50% v/v ethyl acetate in isohexane. There was thus obtained the title compound (580mg)as a clear oil: δ (CDCl3, 300MHz) 2.34 (3 H, s), 3.07 (3 H, s), 4.88 (2 H, s), 6.49-6.58 (3 H, m), 7.18-7.38 (3 H, m), 7.37 (1 H, s), 7.40-7.46 (1 H, m), 7.53-7.54 (1 H, d), 7.74-7.76 (2 H, d), 7.91-7.93 (1 H, d), 8.15-8.19 (1 H, m): MS $[MH]^+$ 392.

Step 4

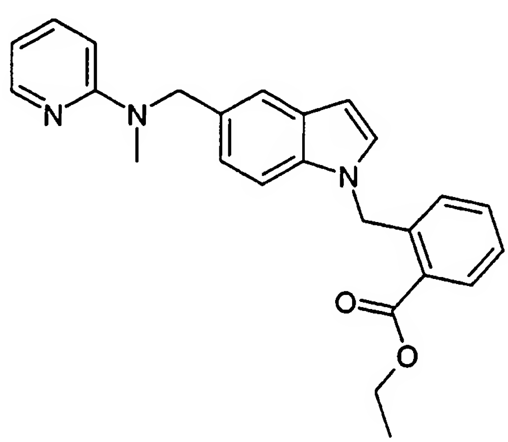
5-methyl-(N-methylamino)-pyridine-indole



1-(*p*-toluenesulfonyl)-5-methyl-(N-methylamino)-pyridine-indole (580mg, 1.48mmol) was dissolved in methanol (40ml) and aqueous 2M sodium hydroxide (5ml, 10.00mmol) was added and heated to 60°C for 48 hours. The reaction was neutralised with 1M aqueous hydrochloric acid and the methanol was evaporated. The residue was partitioned between water and ethyl acetate and the aqueous layer was extracted a further three times with ethyl acetate. The collected organic layers were dried over magnesium sulfate and evaporated. The brown solid obtained was purified by chromatography on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 20% v/v ethyl acetate in isohexane. There was thus obtained the title compound (260mg) as an amorphous white crystalline solid: δ (CDCl3, 300MHz) 3.09 (3 H, s), 4.87 (2 H, s), 6.46-6.59 (3 H, m), 7.15-7.17 (1 H, d), 7.18-7.20 (1 H, m), 7.29-7.31 (1 H, d), 7.38-7.43 (1 H, m), 7.47 (1 H, s), 8.04-8.18 (1 H, s), 8.19-8.20 (1 H, d): MS $[MH]^+$ 236.

Step 5

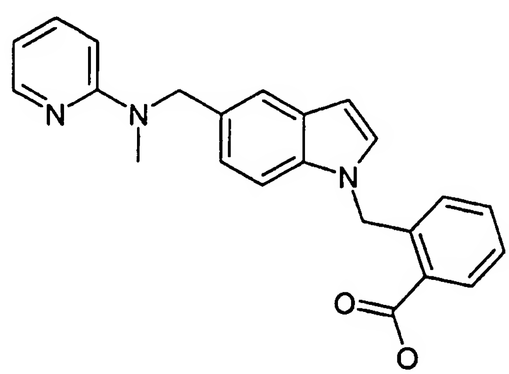
1-(2-carboethoxybenzyl)-5-(2-(N-methyl-N-(2-pyridyl)-aminomethyl)-indole



Sodium hydride (66mg of a 60% dispersion in mineral oil, 1.65mmol) was added to a stirring solution of 5-methyl-(N-methylamino)-pyridine-indole (260mg, 1.10mmol) in N, N-dimethylformamide (5ml). Stirring was continued for three hours. The reaction was then heated to 60°C, ethyl 2-bromomethylbenzoate was added (636mg, 2.42mmol) and the reaction was allowed to stir at this temperature for 16 hours. Subsequently the reaction was added to water (300ml) and neutralised with sodium bicarbonate then extracted four times with diethyl ether. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated. The resulting yellow oil was purified by chromatography on Kieselgel 60 (ART 9385, Merck, Darmstadt) eluting with 10% v/v ethyl acetate in isohexane. There was thus obtained the title compound (330mg)as a clear oil: δ (CDCl3, 300MHz) 1.12-1.15 (3 H, t), 3.09 (3 H, s), 4.38-4.43 (2 H, q), 4.86 (2 H, s), 5.77 (2 H, s), 6.49-6.58 (4 H, m), 7.02-7.04 (1H, d), 7.09-7.17 (2 H, m), 7.28-7.36 (2 H, m), 7.38-7.43 (1 H, m), 7.50 (1 H, s), 8.02-8.04 (1 H, m), 8.18-8.21 (1 H, m); MS $[MH]^+$ 400.

Step 6

1-(2-carboxybenzyl)-5-(2-(N-methyl-N-(2-pyridyl)-aminomethyl)-indole (Compound 5)



1-(2-carboethyoxybenzyl)-5-methyl-(N-methylamino)-pyridine-indole was dissolved in methanol (5ml), 2M aqueous sodium hydroxide (5ml, 10mmol) was added and the mixture stirred for 24 hours at room temperature. The methanol was removed and the aqueous residue acidified with 1M hydrochloric acid. The resultant white solid precipitate was filtered off (101mg). A further crop of product was obtained by extracting the aqueous layer with diethyl ether, evaporating solvent and washing the product with isohexane: δ (d_6-DMSO, 300MHz) 3.14 (3 H, s), 4.89 (2

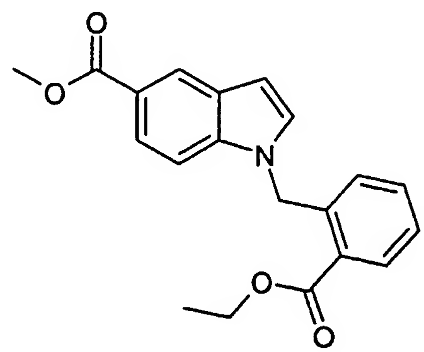
H, s), 5.78 (2 H, s), 6.43-6.49 (2 H, m), 6.68-6.72 (1 H, t), 6.92-7.03 (2 H, m), 7.24-7.49 (5 H, m), 7.66-7.75 (1 H, m), 7.91-7.94 (1 H, m), 8.04-8.05 (1 H, d), 13.22 (1 H, s);MS $[MH]^+$ 372.

Example 26

Preparation of *Ortho*-methoxy Benzyl amide (Compound 13 in Table 1)

Step 1

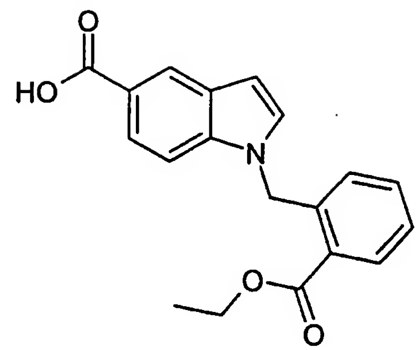
Preparation of diester:



To a solution of 5-carbomethoxy-indole (3.0 g, 17 mmol) in DMF (50 ml) was added NaH (60% in oil, 1.02 g, 25.5 mmol). This was stirred for 15 minutes, and ethyl (2-bromo) benzoate (75%, 4.95 g) added. The mixture was stirred for 45 mins, poured into H_2O, extracted into ether, washed H_2O, dried $MgSO_4$, filtered, solvent removed. Flash column chromatography (SiO_2, EtOAc / isohexane) gave the illustrated **diester** (4.99 g, 87%). NMR d ($CDCl_3$, 300MHz) 1.42 (3H, t), 3.92 (3H, s), 4.41 (2H, q), 5.80 (2H, s), 6.47 (1H, dd), 6.68 (1H, d), 7.18-7.34 (4H, m), 7.86 (1H, dd), 8.06 (1H, dd), 8.44 (1H, d); MS $[MH]^+$ 338;

Step 2

Hydrolysis of methyl ester



To a solution of diester from step 1 (1.0 g, 2.97 mmol) in anhydrous pyridine (5 ml) was added LiI (1.58 g, 11.8 mmol). This was heated to reflux for 20 hours. Solvent was removed and the residue partitioned between 2 M HCl and EtOAc. Water was further extracted with EtOAc. The combined organics were washed with water, brine, dried $MgSO_4$, filtered, solvent removed. Flash column chromatography (SiO_2, Ethyl Acetate / isohexane) gave **3** (355 mg, 37%) as a colourless solid. NMR d ($CDCl_3$, 300MHz) 142 (3H, t), 4.41 (2H, q), 5.82 (2H, s), 6.46-6.51 (1H, m), 6.72 (1H, d), 7.20-7.36 (4H, m), 7.93 (1H, dd), 8.04-8.10 (1H, m), 8.54 (1H, d); MS $[MH]^+$324.

Step 3

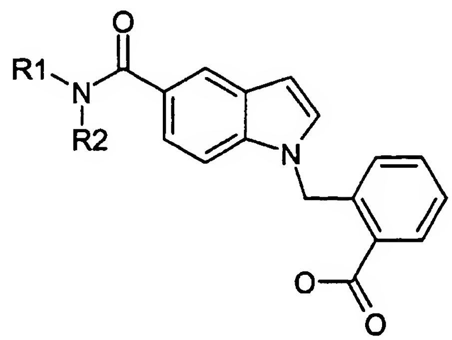
Compound 13

A mixture of 1-(2-Carboethoxybenzyl)-5-carboxyindole (162 mg, 0.5 mmol) and orthomethoxybenzylamine (200 mg, 1.41 mmol), HATU (285 mg, 0.75 mmol) and diisopropylethylamine (350ml, 2.0 mmol) in dimethylformamide (2.5 ml) was stirred for 22 hours. The reaction mixture was partitioned between diethyl ether and 1M aqueous hydrochloric acid. The aqueous phase was further extracted twice with diethyl ether. The combined organics were washed with 1M aqueous hydrochloric acid, dried over magnesium sulfate and the solvent removed. The residue was dissolved in ethanol (5 ml) at 60°C, 1M aqueous lithium hydroxide (1.1 ml, 1.1 mmol) was added and the mixture stirred for 2 hours. The ethanol was removed, and the aqueous residue acidified (35% HCl). The resultant solid precipitate was filtered, washed with water and vacuum dried to an amorphous off-white solid (168 mg):' NMR d (d_6-DMSO, 300MHz) 3.83 (3H, s), 4.45 (2H, d), 5.85 (2H, s), 6.40 (1H, d), 6.65 (1H, d), 6.89 (1H, t), 6.98

(1H, d), 7.17-7.25 (2H, m), 7.33-7.44 (3H, m), 7.53 (1H, d), 7.67 (1H, d), 7.99 (1H, dd), 8.24 (1H, s), 8.72 (1H, t); MS $[MH]^+$ 415.

Example 26

Using a method analogous to that described in Example 25, the following compounds were prepared:



Compd No	MS	NMR
17	371	(d_6-DMSO) 5.85 ("H, s), 6.35-6.44 (1H, m), 6.70 (1H, d), 7.08 (1H, t), 7.28-7.49 (5H, m), 7.57 (1H, d), 7.71 (1H, d), 7.78 (2H, d), 7.93-7.80 (1H, m), 8.28 (1H, s), 10.12 (1H, s), 13.26 (1H, br s);
9		d_6-DMSO) 3.42-3.64 (8H, m), 5.83 (2H, s), 6.49 (1H, dd), 6.70 (1H, d), 7.15 (1H, dd), 7.31-7.41 (3H, m), 7.52 (1H, d), 7.69 (1H, s), 7.96 (1H, dd), 13.14 (1H, br s);
70	403	(d_6-DMSO) 1.97 (2H, p), 3.23 (2H, q), 4.03 (2H, t), 5.87 (2H, s), 6.51 (1H, d), 6.56 (1H, d), 6.89 (1H, s), 7.00 (1H, t), 7.11 (1H, t), 7.21 (1H, s), 7.47 (1H, d), 7.59 (1H, dd), 7.68 (1H, dd), 8.12 (1H, s), 8.33 (1H, t);
71	385	($CDCl_3$) 4.69 (2H, d), 5.80 (2H, s), 6.41-6.47 (2H, m), 6.66 (1H, d), 7.18-7.40 (8H, m), 7.63 (1H, dd), 8.15-8.18 (2H, m);
72	415	(d_6-DMSO) 3.71 (3H, s), 4.41 (2H, d), 5.84 (2H, s), 6.36-6.39 (1H, m), 6.64 (1H, d), 6.88 (2H, d), 7.25 (2H, d), 7.35-

		7.38 (3H, m), 7.52 (1H, d), 7.64 (1H, d), 7.94-7.98 (1H, m), 8.20 (1H, s), 8.84 (1H, t), 13.1 (1H, br s);
73	4194 21	(d_6-DMSO) 4.46 (2H, d), 5.84 (2H, s), 6.36-6.39 (1H, m), 6.65 (1H, d), 7.32-7.39 (7H, m), 7.53 (1H, d), 7.65 (1H, d), 7.94-7.98 (1H, m), 8.21 (1H, m), 8.95 (1H, t);
74	4194 21	(d_6-DMSO) 4.48 (2H, d), 5.85 (2H, s), 6.38 (1H, d), 6.66 (1H, d), 7.28-7.40 (7H, m), 7.54 (1H, d), 7.65 (1H, d), 7.94-7.99 (1H, m), 8.22 (1H, s), 8.87 (1H, t), 13.30 (1H, br s)
75	4194 21	(d_6-DMSO) 4.54 (2H, d), 5.85 (2H, s), 6.37-6.41 (1H, m), 6.66 (1H, d), 7.25-7.44 (7H, m), 7.54 (1H, d), 7.68 (1H, d), 7.89-7.98 (1H, m), 8.24 (1H, s), 8.93 (1H, t);
76	415	(d_6-DMSO) 3.72 (3H, s), 4.45 (2H, d), 5.85 (2H, s), 6.37-6.40 (1H, m), 6.65 (1H, d), 6.79 (1H, dd), 6.88-6.91 (2H, m), 7.23 (1H, t), 7.35-7.40 (3H, m), 7.53 (1H, d), 7.65 (1H, dd), 7.94-7.978 (1H, m), 8.22 (1H, s), 8.88 (1H, t), 13.23 (1H, br s);
77	399	(d_6-DMSO) 2.85 (2H, t), 3.42-3.52 (2H, m), 5.84 (2H, s), 6.37-6.41 (1H, m), 6.63 (1H, d), 7.16-7.40 (8H, m), 7.52 (1H, d), 7.58 (1H, d), 7.94-7.97 (1H, m), 8.13 1H, s), 8.43 (1H, t);
78	445	(d_6-DMSO) 3.71 (3H, s), 3.72 (3H, s), 4.41 (2H, d), 5.84 (2H, s), 6.37-6.40 1H, m), 6.64 (1H, d), 6.89 (1H, d), 6.93 (1H, d), 7.00 (1H, s), 7.32-7.39 (2H, m), 7.53 1H, d), 7.64 (1H, d), 7.94-7.97 (1H, m), 8.20 (1H, s), 8.83 (1H, t), 13.13 (1H, br s);
79	453	(d_6-DMSO) 4.56 (2H, d), 5.85 (2H, s), 6.37-6.40 (1H, m), 6.65 (1H, d), 7.33-7.40 (3H, m), 7.53-7.55 (3H, m), 7.65-7.70 (3H, m), 7.95-7.98 (1H, m), 8.23 (1H, s), 9.02 (1H, t), 13.20 (1H, br s);
80	435	(d_6-DMSO) 4.96 (2H, d), 5.85 (2H, s), 6.36-6.39 (1H, m), 6.64 (1H, d), 7.35-7.57 (8H, m), 7.69 (1H, d), 7.84 (1H, dd), 7.97-7.99 (2H, m), 8.19-8.25 (2H, m), 8.95 (1H, t), 13.23 (1H, br s);

81	469	
82	453	(d_6-DMSO) 4.56 (2H, d), 5.85 (2H, s), 6.36-6.40 (1H, m), 6.66 (1H, d), 7.34-7.41 (3H, m), 7.53-7.72 (6H, m),. 7.94-7.97 (1H, m), 8.21 (1H, s), 9.01 (1H, t), 13.30 (1H, br s);
83	429	(d_6-DMSO) 4.22-4.24 (4H, m), 5.87 (2H, s), 6.37-6.42 (1H, m), 6.69 (1H, d), 6.80 (1H, d),. 7.21 (1H, dd), 7.33-7.44 (4H, m), 7.54-7.57 (1H, m), 7.68 (1H, d), 7.97 (1H, d), 8.25 (1H, s), 9.96 (1H, s), 13.20 (1H, br s);
84	377	(d_6-DMSO) 1.03-1.38 (5H, m), 1.55-1.80 (3H, m), 3.77 (1H, br), 5.84 (2H, s), 6.33-6.37 (1H, m), 6.63 (1H, d), 7.32-7.37 (3H, m), 7.51 (1H, d), 7.60 (1H, d), 7.96 (1H, dd), 8.03 (1H, d), 8.03 (1H, d), 8.15 (1H, s), 13.25 (1H, br s);
50	422	(d_6-DMSO) 5.90 (2H, d), 6.42 (1H, dd), 6.74 (1H, d), 7.37-7.68 (6H, m), 7.80 (1H, d), 7.94-7.98 (3H, m), 8.39 (1H, s), 8.87 (1H, d), 9.18 (1H, d), 10.60 (1H, s), 13.31 (1H, br s);
30	428	
40	411	(d_6-DMSO) 2.97 (2H, dd), 3.23 (2H, dd), 4.62-4.78 (1H, m), 5.84 (2H, s), 6.35-6.39 (1H, m), 6.63 (1H, d), 7.13-7.16 (2H, m), 7.21-7.24 (2H, m), 7.34-7.37 (3H, m), 7.52 (1H, d), 7.63 (1H, d), 7.94-7.97 (1H, m), 8.18 (1H, s), 8.50 (1H, d), 13.24 (1H, br s);
41	463	(d_6-DMSO) 3.18 (3H, s), 4.58 (2H, d), 5.85 (2H, s), 6.36-6.40 (1H, m), 6.66 (1H, d), 7.35-7.40 (3H, m), 7.53-7.59 (3H, m), 7.66 (1H, d), 7.88 (2H, d), 7.94-7.98 (1H, m), 8.23 (1H, s), 9.04 (1H, t), 13.24 (1H, br s);
26	351	(d_6-DMSO) 0.90 (3H, t), 1.29-1.36 (2H, m), 1.45-4.54 (2H, m), 3.26 (2H, q), 5.84 (2H, s), 6.36-6.39 (1H, m), 6.63 (1H, d), 7.33-7.35 (3H, m), 7.52 (1H, d), 7.59 (1H, d), 7.94-7.97 (1H, m), 8.14 (1H, s), 8.27 (1H, t), 13.21 (1H, br s);
27	475	(d_6-DMSO) 4.54 (4H, br s), 5.82 (2H, s), 6.40-6.45 (1H, m), 6.58 (1H, d), 7.16-7.44 (14H, m), 7.51 (1H, d), 7.76 (1H, s),

		7.93-7.97 (1H, m), 13.15 (1H, br s);
28	429	(d_6-DMSO) 4.38 (2H, d), 5.84 (2H, s), 5.97 (2H, s), 6.35-6.39 (1H, m), 6.79 (1H, d), 6.85 (1H, d), 6.92 (1H, d), 7.33-7.39 (1H, m), 7.53 (1H, d), 7.94-7.98 (1H, m), 8.20 (1H, s), 8.84 (1H, t), 13.21 (1H, br s);
29	391	(d_6-DMSO) 4.63 (2H, d), 5.84 (2H, s), 6.36-6.39 (1H, m), 6.58 (1H, d), 6.92-9.97 (1H, m), 7.01 (1H, d), 7.37-7.40 (3H, m), 7.53 (1H, d), 7.67 (1H, d), 7.94-7.97 (1H, m), 8.19 (1H, s), 9.00 (1H, t), 13.20 (1H, br s);
48	422	(d_6-DMSO) 5.89 (2H, s), 6.42 (1H, d), 6.73 (1H, d), 7.36-7.51 (4H, m), 7.59 (1H, d), 7.77 (1H, d), 7.96-8.01 (2H, m), 8.08 (1H, dd), 8.32 (1H, d), 8.36 (1H, s), 8.57 (1H, s), 8.80 (1H, d), 10.47 (1H, s), 13.25 (1H, br s);

Example 27

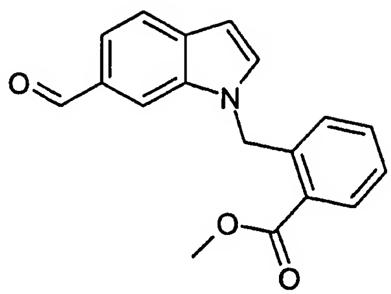
Preparation of Compound 49 in Table 1

To a solution of ethyl ester from Example 24 step 2 (74 mg, 0.23 mmol) in ethanol (3 ml) at room temperature was added 1M aqueous sodium hydroxide solution (3 ml). After stirring for 3 hours the solvent was removed, water was added and the solution acidified with c. HCl. The resultant colourless precipitate was filtered off and washed with water to give the desired compound (50 mg, 74%) as an amorphous colourless solid. NMR d ($CDCl_3$/d_6-DMSO, 300MHz) 5.70 (2H, s), 6.30-6.37 (1H, m), 6.52 (1H, d), 7.05 (1H, d), 7.11 (1H, d), 7.17 (1H, t), 7.73 (1H, d), 7.96 (1H, t), 8.29 (1H, s); MS $[M-1]^-$ 294.

Example 28

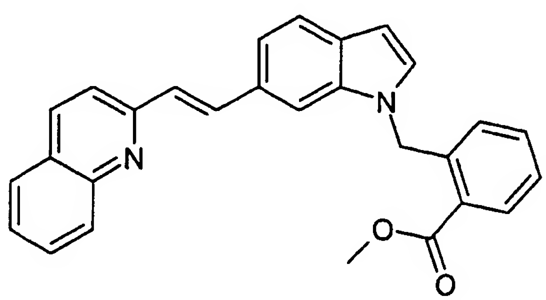
Preparation of Compound 17 in Table 1

Step 1



A mixture of 6-formylindole (2.43 g, 16.7 mmol) and methyl-2-bromomethyl-benzoic acid (5.8 ml) in and K_2CO_3 in 35 ml DMF was stirred at room temperature fo r18 hours. The mixture was poured into water and extracted three times with ether. The combined organics were dried over $MgSO_4$, filtered and the solvent removed. Flash Column Chromatography (EtOAc / isohexane) gave 1-(2-Carbomethoxybenzyl)-6-formyl-indole (3.98 g, 81%) as a red solid. NMR d ($CDCl_3$, 300MHz) 3.95 (3H, s), 5.87 (2H, s), 6.49 (1H, dd), 6.66 (1H, d), 7.28-7.37 (3H, m), 7.64 (1H, d), 7.73-7.80 (2H, m), 8.04-8.09 (1H, m), 9.97 (1H, s); MS $[MH]^+$ 294.

Step 2



2-Quinoline methylene triphenylphosphonyl bromide (440 mg, 1.0 mmol) and 1-(2-Carbomethoxybenzyl)-6-formyl-indole were dissolved in tetrahydrofuran (20 ml) at 0°C. A 1M solution of potassium *tert*-butoxide in *tert*-butanol (1.0 ml, 1.0 mmol) was added dropwise and the mixture stirred at room temperature for 16 hours before pouring into water and extracting

into ether. Flash column chromatography (EtOAc/isohexane) gave 1-(2-Carbomethoxybenzyl)-6-(2-quinolylstyryl)-indole (100 mg, 27%) as a yellow solid. NMR d (d_6-DMSO, 300MHz) 3.92 (3H, s), 5.86 (2H, s), 6.44 (1H, d), 6.60 (1H, d), 7.37-7.99 (13H, m), 8.22 (1H, d), 8.29 (1H, d); MS $[MH]^+$ 419.

Step 3

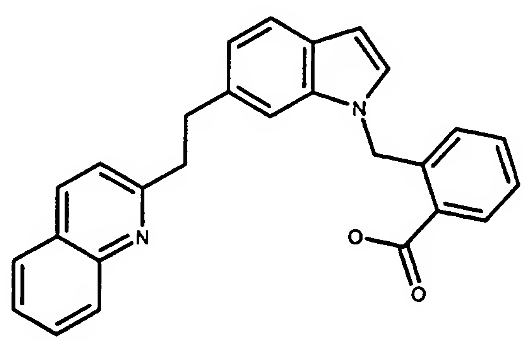
Compound 17

To a solution of 1-(2-Carbomethoxybenzyl)-6-(2-quinolylstyryl)-indole (60 mg, 0.15 mmol) in methanol was added 2M aqueous NaOH solution (100 ml, 0.2 mmol). The mixture was heated to 60°C for 18 hours, cooled, and the methanol removed. Water was added, and the mixture acidified with the addition of 2M aqueous HCl and neutralised with saturated aqueous sodium hydrogen carbonate solution. The resulting red solid precipitate was filtered to give compound 2 (8 mg, 14%) as a red solid. NMR d ($CDCl_3$ + TFA, 300MHz) 5.92 (2H, s), 6.38 (1H, d), 6.69 (1H, d), 7.33-8.45 (14H, m), 8.97 (1H, d; MS $[MH]^+$ 406.

Example 29

Preparation of Compound 30 in Table 1

Step 1



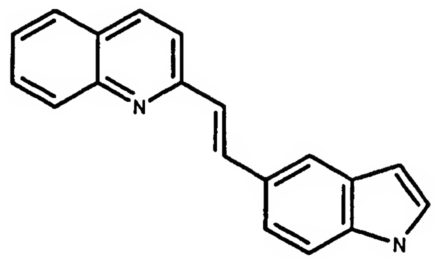
To a suspension of product Example 28, step 2 (250 mg, 0.56 mmol) in tetrahydrafuran (7 ml) and methanol (5 ml), was added sufficient sodium hydroxide to cause solvation. The solution was placed in a hydrogen atmosphere overnight in the presence of 10% Pd/C (52 mg). The reaction was filtered through celite® and the solvent was removed under reduced pressure. The residue was dissolved in methanol (5 ml) and acidified to pH 1 with 1N HCl . The resulting mixture was stirred for 1 hour at room temperature, then 45 minutes at 40°C, filtered off, washed with water and dried under vacuum at 50°C. The product was obtained (192 mg, 75 %) as a

yellow solid, melting point 115-120°C. MS $[MH]^+$ 407; required for $C_{27}H_{22}N_2O_2$.HCl.0.75H_2O): C: 71.04; H: 5.41; N: 6.14. Found C: 71.15; H: 5.27; N: 6.11.

Example 30

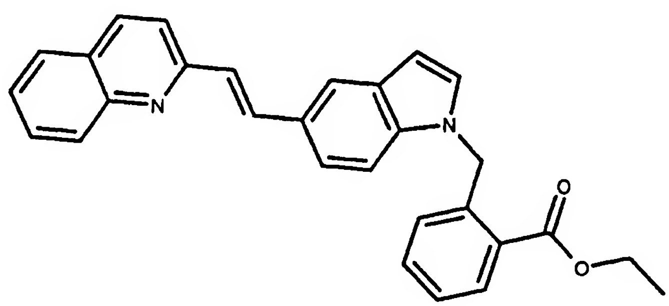
Preparation of Compound 2 in Table 1

Step 1



2-Quinoline methylene triphenylphosphonyl bromide (4.17 g, 8.6 mmol) and 5-formyl-indole were dissolved in THF (20 ml) at 0°C. A 1M solution of potassium *tert*-butoxide in THF(8.6 ml, 8.6 mmol) was added dropwise at 0°C and the mixture stirred at room temperature for 16 hours before pouring into 1N HCl (100 ml) and EtOAc (100 ml). This was filtered, washed with water, suspended in MeOH and 6N HCl (1 ml), filtered, washed with water and dried under vacuum at 65°C to yield 5-(2-quinolylstyryl)-indole (1.79 g, 84%) as a red solid, melting point 265-268°C.

Step 2

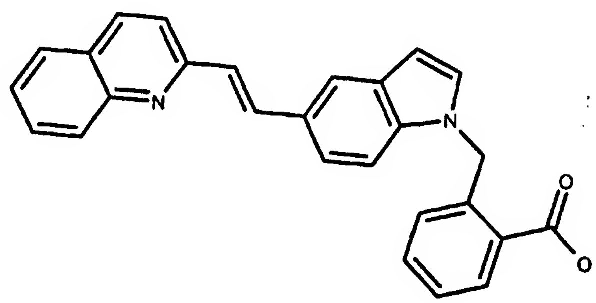


A mixture of 5-(2-quinolylstyryl)-indole (500 mg, 1.63 mmol) and sodium hydride (130.4 mg 60% dispersion in oil, 3.26 mmol) in DMF (20 ml) was stirred for 30 minutes. Ethyl-2-chloromethyl-benzoic acid (357.6 mg, 1.80 mmol) was added and the reaction was stirred at room temperature for 18 hours. The mixture was poured into water and extracted three times with ether. The combined organics were dried over $MgSO_4$, filtered and the solvent removed

under reduced pressure. Flash Column Chromatography (EtOAc / isohexane) gave 1-(2-Carboethoxybenzyl)-5-(2-quinolylstyryl)-indole (690 mg, 97%) as a pale yellow gum solid.

Step 3

Compound 2

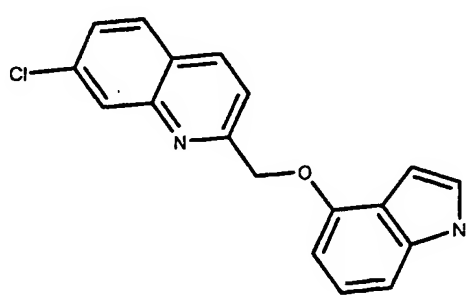


To a solution of 1-(2-Carboethoxybenzyl)-5-(2-quinolylstyryl)-indole (680 mg, 1.57 mmol) in methanol (20ml), water (10 ml) and THF (30 ml) was added aqueous LiOH solution (395.8 mg, 9.43 mmol). The mixture was stirred at room temperature for 18 hours, cooled, and the methanol removed. The mixture was acidified by the addition of 2M aqueous HCl and the resulting red solid precipitate was filtered to yield compound 2 (561.2 mg, 81%) as an orange solid; Required for $C_{27}H_{20}N_2O_2$.HCl.0.20H_2O): C: 72.95; H: 4.85; N: 6.30. Found C: 72.99; H: 5.01; N: 6.15.

Example 31

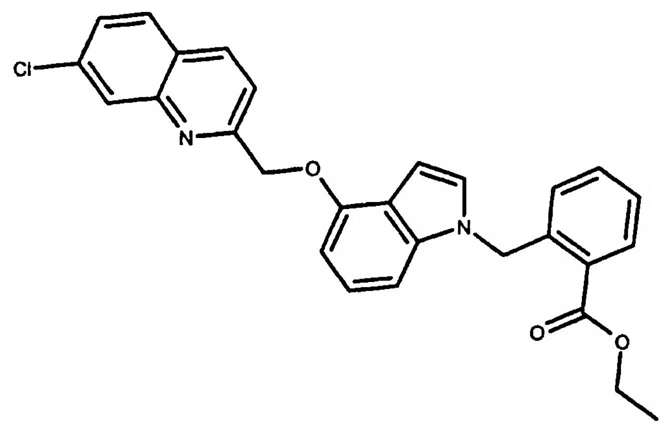
Preparation of Compound 31 in Table 1

Step1



A mixture of 4-hydroxyindole (500 mg, 3.76 mmol) anhydrous ground potassium carbonate (1.56 g, 11.28 mmol)and 7-chloro-2-bromomethyl-quinoline (1.15 g, 4.5 mmol) was dissolved in DMF (20 ml) and stirred at 50°C for 5 hours. The reaction was poured onto water and extracted with EtOAc. The organics were dried over magnesium sulfate and dried under reduced pressure. Chromatography on silica with EtOAc / toluene as eluent afforded a solid which was recrystallised form toluene to yield 7-chloro-2-methyl-quinoline-4-hydroxyindole (733 mg, 63 %) as an off white solid, melting point 173°C.

Step 2



A mixture of 7-chloro-2-methyl-quinoline-4-hydroxyindole (200 mg, 0.65 mmol) and sodium hydride (29.0 mg 60% dispersion in oil, 0.71 mmol) in DMF (10 ml) was stirred for 30 minutes. Ethyl-2-chloromethyl-benzoic acid (141.0 mg, 0.71 mmol) was added and the reaction was stirred at room temperature for 5 hours. The mixture was poured into water and extracted three times with ethyl acetate. The combined organics were washed with water and a saturated solution of sodium chloride, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash Column Chromatography (EtOAc / isohexane) gave 1-(2-Carboethoxybenzyl)-4-(7-chloro-2-methyl-quinoline)-hydroxyindole as a yellow solid, melting point 127°C, MS $[MH]^+$ 470.

Step 3

Compound 31

To a solution of 1-(2-Carboethoxybenzyl)-4-(7-chloro-2-methyl-quinoline)-hydroxyindole (from step 2) in methanol (5ml) and THF (5 ml) was added 2M aqueous LiOH solution (2 M). The

reaction was stirred at room temperature for 18 hours and added to water (76 ml) containing 6N HCl (6.1 ml), then stirred for 15 minutes. The resulting yellow solid precipitate was filtered off and washed with water, then in dried under vacuum at 50°C to yield compound 31 (184 mg, 0.41 mmol), melting point 230-233°C; Required for $C_{26}H_{18}N_2O_3$.HCl.): C: 65.15; H: 4.21; N: 5.84. Found C: 65.49; H: 4.37; N: 5.66.

Example 32

Biological Assays

(a) Ligand binding assay

The assay was based on a scintillation proximity assay in which the displacement of radiolabelled [^{3}H] BRL 49653 (rosiglitazone) binding from biotinylated human PPARγ-recombinant protein was measured. The PPARγ ligand binding domain (LBD) of human PPARγ1 was expressed in *E-Coli* as a poly his and *c-myc* tagged fusion protein. Compounds of the invention were incubated with [^{3}H] BRL 49653, 30nM (0.1mCi), biotinylated human PPARg LBD protein (150 ng) and streptavidin SPA beads, 0.25 mg/well. Compounds were able to displace radiolabel and so have pharmacological potential as PPARg agonists or antagonists.

(B) Cell transactivation assays:

Assays were performed by transient transfection of Hepa1c1c7 cells in which compounds of the invention were tested for their ability to activate human PPARa, d and g isoforms. Cells were co-transfected with either PPARa, d and g expression vectors (containing the entire ORF sequence) and a reporter construct carrying a PPRE linked Lac Z construct. Cells were transfected using Superfect and cultured in T75 flasks overnight, then plated into 96 well plates and left for 5 hours before the addition of test compound. After a further 24 hours PPAR activation was quantitated indirectly as β-Galactosidase activity by hydrolysis of chlorophenol red-β-D-galactopyranoside (CPRG), measured spectrophotometrically at 580 nm. Compounds of the invention were active in this assay. For example Compound 3 in Table 1 showed a g transactivation of 79% at a concentration of 10μM.

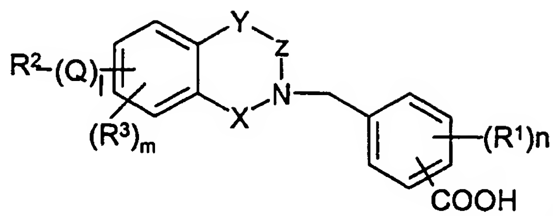
According to their activity in transactivation assays and by comparison to the selective PPARg agonist, BRL 49653; compounds of the invention were categorised as either having pharmacological properties consistent with: selective PPARg agonists, partial agonists or non-selective PPAR a/g agonists.

Adipocyte differentiation assay:

3T3L1 preadipocytes were grown in DMEM containing 10% NBCS and 1 day post-confluence cells were cultured in differentiation medium (DMEM containing 5% FCS, 1 μg/ml insulin, 0.25μM dexamethasone and 0.5mM IBMX) in the presence or absence of compounds. BRL 49653 was used as the positive control and the medium replenished after 3 days. On day 7, cells were lysed and glycerophosphate dehydrogenase activity measured spectrophotometrically at 340nm. Under the conditions of the assay BRL 49653 induces a dose related increase in glycerophosphate dehydrogenase activity. Compounds of the invention were found to activate PPARg in the transactivation assay (vide supra) induce glycerophosphate dehydrogenase activity in 3T3L1 cells in a dose -related manner. For example, Compound 3 in Table 1 showed activity at 81% as compared to the control at a concentration of 10μM.

CLAIMS:

1. A use of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt or ester thereof, in the preparation of a medicament for use in the activation of PPAR,

X, Y and Z may represent either bonds or atoms or groups of atoms such that X, Y and Z together with the nitrogen atom complete an optionally substituted five or six-membered aromatic or non-aromatic ring;

where each R^1 is selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl, C_{1-3}alkoxy, optionally substituted hydrocarbyl or optionally substituted heterocyclyl and n is 0, 1 or 2;

R^2 is selected from R^4, OQR^4, $C(O)_pR^4$, $S(O)_qR^4$, $N(QR^6)R^7$, halo, cyano, carboxy, nitro, $(O)CN(QR^6)R^7$, $OC(O)N(QR^6)R^7$, $NR^5C(O)_pR^6$, $NR^5CON(QR^6)R^7$, $NR^5CSN(QR^6)R^7$, $NR^5C(O)OR^6$, $N{=}CR^6R^7$, $S(O)_qN(QR^6)R^7$ or $NR^5S(O)_qR^6$, or R^2 is carboxy, $CH{=}CHQR^4$ or $NR^5C(O)C(O)R^6$;

where p is 1 or 2, q is 0, 1, 2 or 3;

R^4 is selected from optionally substituted hydrocarbyl or optionally substituted -Q-heterocyclyl groups;

R^5, R^6 and R^7 are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted Qheterocyclyl groups or R^6 and R^7 together with the atom to which they are attached form a ring which may be optionally substituted and which may comprise one or more heteroatoms;

l is 0 or 1;

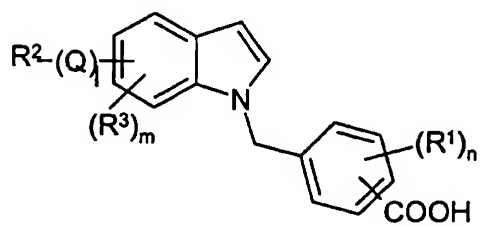
each Q is independantly selected from a direct bond, C_{1-3}alkylene or C_{2-3}alkenylene;

each R^3 is independently selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl, C_{1-3}alkoxy and m is 0, 1 or 2.

2. Use of a compound as claimed in claim 1 wherein X is a bond or a group CH_2 or C(0); Y-Z- is selected from -CHR^{17}-CHR^{18}-C(O)-, -CHR^{17}-CHR^{18}-CHR^{19}-, where R^{17}, R^{18} and R^{19} are independently selected from hydrogen or C_{1-3} alkyl.

3. Use of a compound as claimed in claim 1 or claim 2 wherein R^{17}, R^{18}, and R^{14} are all hydrogen.

4. Use of a compound as claimed in any claim from 1 to 3 wherein where X-Y-Z form an indole group as shown below

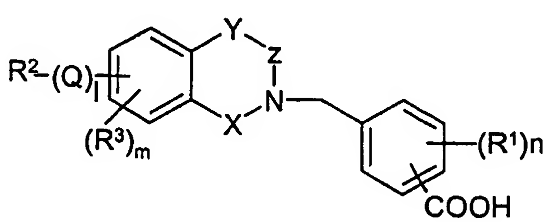


(IA)

and A, l, R^1, R^2, R^3, m and n are as defined in claim 1, 2 or 3.

5. Use of a compound as claimed in any claim from 1 to 3 wherein at all occurences Q is a direct bond and R^2 is not carboxy, CH=CHQR^4 or NR^{5}C(O)C(O)R^6.

6. A compound of formula (IA)



(IA)

or a pharmaceutically acceptable salt or ester thereof,

where X is a bond or a group CH_2 or C(O); and -Y-Z- is selected from -CR^{17}=CR^{18}-, -C(O)-CR^{17}=CR^{18}-, -CR^{17}=CR^{18}C(O)-, -CHR^{17}-CHR^{18}-C(O)-, -CHR^{17}-CHR^{18}-CHR^{19}-, where R^{17}, R^{18} and R^{19} are independently selected from hydrogen or C_{1-3}alkyl;

where each R^1 is selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl, C_{1-3}alkoxy, optionally substituted hydrocarbyl or optionally substituted heterocyclyl and n is 0, 1 or 2;

R^2 is selected from R^4, OQR^4, $C(O)_pR^4$, $S(O)_qR^4$, $N(QR^6)R^7$, halo, cyano, carboxy, nitro, $(O)CN(QR^6)R^7$, $OC(O)N(QR^6)R^7$, $NR^5C(O)_pR^6$, $NR^5CON(QR^6)R^7$, $NR^5CSN(QR^6)R^7$, $NR^5C(O)OR^6$, $N{=}CR^6R^7$, $S(O)_qN(QR^6)R^7$ or $NR^5S(O)_qR^6$, or R^2 is carboxy, $CH{=}CHQR^4$ or $NR^5C(O)C(O)R^6$;

where p is 1 or 2, q is 0, 1, 2 or 3;

R^4 is selected from optionally substituted hydrocarbyl or optionally substituted -Q-heterocyclyl groups;

R^5, R^6 and R^7 are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted Qheterocyclyl groups or R^6 and R^7 together with the atom to which they are attached form a ring which may be optionally substituted and which may comprise one or more heteroatoms;

l is 0 or 1;

each Q is independantly selected from a direct bond, C_{1-3}alkylene or C_{2-3}alkenylene;

each R^3 is independently selected from C_{1-3}alkyl, halo, haloC_{1-3}alkyl, C_{1-3}alkoxy and m is 0, 1 or 2; provided that

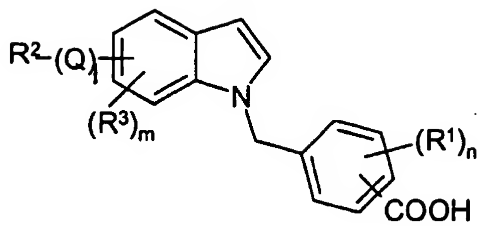
(i) where the group of sub-formula (a) as defined above is a group of sub-formula (h) and R^{17} and R^{18} are hydrogen, R^2 is other than (2-ethyl-5,7-dimethyl-3H imidazo [4,5-b]pyridin-3-yl)methyl, or methyl substituted with an aromatic heterocyclic ring containing 2 or 3 nitrogen atoms;

(ii) where the group of sub-formula (a) as defined above is a group of sub-formula (g) as defined above and R^{17} and R^{18} are hydrogen, R^2 is other than a group $S(O)_qNR^6R^7$ where q is 2, R^6 is hydrogen and R^7 is 2-chlorophenyl; or

(iii) where the group of sub-formula (a) is a group of sub-formula (i) as defined above and R^{17} and R^{18} are hydrogen, either R^2 is other than halo, cyano, nitro, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, optionally substituted phenyl or a group OR^{14}, $NR^{14}R^{15}$ or SR^{14} where R^{14} and R^{15} are selected from hydrogen, C_{1-5}alkyl, C_{2-5}alkenyl or C_{2-5}alkynyl or optionally substituted phenyl, or m is other than 0.

7. A compound of formula (1A) as claimed in claim 6 or 7 wherein R^{17}, R^{18}, and R^{19} are all hydrogen.

8. A compound of Formula (1A) as claimed in claim 6 or claim 7 where X-Y-Z form an indole group as shown below



(IA)

wherein A, l, R^1, R^2, R^3, m and n are as defined in claim 6;

provided that where the group of sub-formula (a) as defined above is a group of sub-formula (h) and R^{17} and R^{18} are hydrogen, R^2 is other than (2-ethyl-5,7-dimethyl-3H imidazo [4,5-b]pyridin-3-yl)methyl, or methyl substituted with an aromatic heterocyclic ring containing 2 or 3 nitrogen atoms.

9. A compound of Formula (1A) as claimed in claim 6, 7 or 8 wherein R^5, R^6 and R^7 are independently selected from hydrogen;

a hydrocarbyl which is alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl groups optionally substituted by a group selected from halo, cyano, nitro, $C(O)_aR^8$, OR^8, $S(O)_bR^8$, NR^9R^{10}, $C(O)NR^9R^{10}$, $OC(O)NR^9R^{10}$, $-NR^8C(O)_aR^9$, $-NR^8CONR^9R^{10}$, $N{=}CR^9R^{10}$, $S(O)_bNR^9R^{10}$ and $NR^8S(O)_bR^{10}$ where a is 1 or 2 and b is 0, 1, 2 or 3 (where R^8, R^9 and R^{10} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl, any of which may themselves be optionally substituted by halo, nitro cyano, alkanoyl such as acetyl, oxo, carboxy or salts or esters thereof, alkoxy such as methoxy, ethoxy or propoxy, aryloxy such as phenoxy, thioalkyl such as thiomethyl, thioethyl or thiopropyl, sulphate, haloalkyl, aryl, carbamate, amino, mono- or di-alkyl amino, aryl, heterocyclyl or aralkyl groups);

a Qheterocyclyl, where Q is defined in claim 1, which is a single or fused ring structure which may be aromatic or non-aromatic in nature and which contains from 2 to 20 ring atoms, at least one of which is a heteroatom, optionally substituted with a group selected from those listed above for hydrocarbyl group, as well as alkyl, alkenyl or alkynyl groups which may be optionally substituted with halo, cyano, nitro, $C(O)_aR^{11}$, OR^{11}, $S(O)_bR^{11}$, $NR^{12}R^{13}$, $C(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{13}$, $-NR^{11}C(O)_aR^{12}$, $-NR^{11}CONR^{12}R^{13}$, $-N{=}CR^{12}R^{13}$, $S(O)_bNR^{12}R^{13}$ or $-NR^{11}S(O)_bR^{12}$ where R^{11}, R^{12} and R^{13} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl, and a and b are as defined above;

or R^6 and R^7 together with the atom to which they are attached form a ring which may be optionally substituted and which may comprise one or more heteroatoms.

10. A compound as claimed in any claim from 6 to 8 wherein at all occurences Q is a direct bond and R^2 is not carboxy, $CH{=}CHQR^4$ or $NR^5C(O)C(O)R^6$.

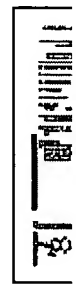
11. A compound of Formula (IA), as defined in any claim from 7 to 9, for use as a medicament.

12. A pharmaceutical composition comprising a compound of formula (IA), as defined in any claim from 7 to 9, in combination with a pharmaceutically acceptable carrier.

The Delphion Integrated View

Title: **WO0112187A2: CHEMICAL COMPOUNDS**[French]

Derwent Title: New and known benzoic acid derivatives are peroxisome proliferator activator (PPAR) agonists, useful for treating diabetes [Derwent Record]



Country: **WO** World Intellectual Property Organization (WIPO)

Kind: **A2** Publ.of the Int.Appl. without Int.search REP. i (See also: WO0112187A3)

Inventor: **HARGREAVES, Rodney, Brian**; Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom
WHITTAMORE, Paul, Robert, Owen; Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom

Assignee: **ASTRAZENECA UK LIMITED**, 15 Stanhope Gate, London W1Y 6LN, United Kingdom
News, Profiles, Stocks and More about this company

Published / Filed: **2001-02-22** / 2000-08-14

Application Number: **WO2000GB0003140**

IPC Code: A61K 31/404;

ECLA Code: **A61K31/404**; A61K31/4439; A61K31/4704; A61K31/4709; C07D209/08; C07D215/20; C07D215/22B; C07D401/06+215+209C; C07D401/12+215+209C; C07D401/12+213+209C; C07D401/12+217+209C; C07D405/04+307+209C; C07D405/12+317+209C; C07D405/12+319+209C; C07D409/12+333B+209C; C07D413/12+261+209C; C07D417/12+285B+209C; C07D521/00B1N3;

Priority Number: 1999-08-18 **GB1999000019411**

Abstract: The present invention relates to the use of certain benzoic acid derivatives of formula (I), where the substituents are as defined in the specification, which act as peroxisome proliferator activated receptor (PPAR) agonists, in particular gamma receptors (PPAR gamma), and so are useful in the treatment of states of insulin resistance, including type 2 diabetes mellitus. [French]

Attorney, Agent or Firm: **BROWN, Andrew, Stephen** ;

INPADOC Legal Status: Show legal status actions Get Now: Family Legal Status Report

Designated Country: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW, **European patent:** AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE, **OAPI patent:** BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG, **ARIPO patent:** GH GM KE LS MW MZ SD SL SZ TZ UG ZW, **Eurasian patent:** AM AZ BY KG

KZ MD RU TJ TM

Family: Show 16 known family members

First Claim: CLAIMS:
Show all claims

Description
Expand description

+ - I - CHEMICAL COMPOUNDS The present invention relates to the use of certain benzoic acid derivatives which act as peroxisome proliferator activated receptor (PPAR) agonists, in particular gamma receptors (PPARy), and so are useful in the treatment of states of insulin resistance, including type 2 diabetes mellitus. Novel pharmaceutical compositions and novel compounds are also defined, together with methods of their production.

Traditionally, therapeutic intervention in type 2 diabetes has had a 'glucocentric focus' dominated by the use of insulin secretogogues e.g. the sulphonylureas and the measurement of glycated haemoglobin (HbAlc) or fasting blood sugar level (FPG) as indices of diabetic control.

Forward References: **Go to Result Set:** Forward references (1)

PDF	Patent	Pub.Date	Inventor	Assignee	Title
	US6943169	2005-09-13	Repke; David Bruce	Roche Palo Alto LLC	Quinolinone uses thereof

Other Abstract Info: None